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JCS/JSCVS 2018 Guideline on Revascularization of Stable Coronary Artery Disease

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Refer to **Appendix 2** for the details of members.

JCS Joint Working Group: The Japanese Circulation Society, The Japanese Coronary Association, The Japanese Society for Cardiovascular Surgery, Japanese Association for Coronary Artery Surgery, The Japanese Association for Thoracic Surgery, Japanese Association of Cardiovascular Intervention and Therapeutics, and Japanese College of Cardiology.

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Abbreviations

AC	aorto-coronary
ACC	American Collage of Cardiology
ACCF	American College of Cardiology Foundation
ACE-I	angiotensin converting enzyme inhibitor
ACS	acute coronary syndrome
ACT	activated clotting time
AHA	American Heart Association
AS	aortic stenosis
AUC	appropriate use criteria
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BITA	bilateral internal thoracic artery
BMS	bare metal stent
BRS	bioresorbable scaffold
CABG	coronary artery bypass grafting
CFVR	coronary flow velocity reserve
CIN	contrast induced nephropathy
CKD	chronic kidney disease
CTA	computed tomography angiography
CTO	chronic total occlusion
DAPT	dual antiplatelet treatment
DCA	directional coronary atherectomy
DCB	drug coated balloon
DES	drug eluting stent
DFI	diastolic filling index
DM	diabetes mellitus
DOAC	direct oral anticoagulants
EACTS	European Association for Cardio-Thoracic Surgery

EES	everolimus-eluting stent
ELCA	excimer laser coronary angioplasty
EPA	eicosapentaenoic acid
ESC	European Society of Cardiology
ESVI	end-systolic volume index
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFR	fractional flow reserve
GEA	gastroepiploic artery
GFR	glomerular filtration rate
HCR	hybrid coronary revascularization
HIT	heparin-induced thrombocytopenia
HR	hazard ratio
IABP	intra-aortic balloon pump
ICER	incremental cost-effectiveness ratio
ICG	indocyanine green
IFI	intraoperative fluorescence imaging
iFR	instaneous wave-free ratio
ITA	internal thoracic artery
IVUS	intravascular ultrasound
LAD	left anterior descending coronary artery
LCA	left coronary artery
LCX	left circumflex coronary artery
LGE	late gadolinium enhancement
LITA	left internal thoracic artery
LMCA	left main coronary artery
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiac or cerebrovascular event

MACE	major adverse cardiovascular event
MIDCAB	minimally invasive direct coronary artery bypass
MR	mitral regurgitation
OCT	optical coherence tomography
OFDI	optical frequency domain imaging
OMT	optimal medical therapy
ONCAB	on-pump coronary artery bypass
OPCAB	off-pump coronary artery bypass
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PEEP	positive end expiratory pressure
PES	paclitaxel-eluting stent
PI	pulsatility index
POBA	plain old balloon angioplasty
PT-INR	prothrombin time-international normalized ratio
QALY	quality-adjusted life year
RA	radial artery
RCA	right coronary artery
RCT	randomized controlled trial
RITA	right internal thoracic artery
SCAI	Society for Cardiovascular Angiography and Interventions
SES	sirolimus-eluting stent
SITA	single internal thoracic artery
STS	Society of Thoracic Surgeons
SV	saphenous vein
SVG	saphenous vein graft
SVR	surgical ventricular reconstruction
TAVI	transcatheter aortic valve implantation
TLR	target legion revascularization
TTFM	transit-time flowmetry
VLST	very late stent thrombosis

Acronyms of Clinical Trials

ABACAS	Adjunctive Balloon Angioplasty After Coronary Atherectomy Study
ABSORB	A Bioresorbable Everolimus-Eluting Scaffold Versus a Metallic Everolimus-Eluting Stent
ACCOMPLISH	Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AFIRE	Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease
ART	Arterial Revascularisation Trial
ARTS	Arterial Revascularization Therapies Study
ASCERT	American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BARI (2D)	Bypass Angioplasty Revascularization Investigation (2 Diabetes)
BASKET-SMALL	Basel Kosten Effektivitäts Trial – Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions
BCIS-I	Balloon Pump Assisted Coronary Intervention Study
BENESTENT	Belgium Netherlands Stent
BEST	Trial of Everolimus-Eluting Stents or Bypass Surgery for Coronary Disease
BIP	Bezafibrate Infarction Prevention
CANVAS	Canagliflozin Cardiovascular Assessment Study
CASCADE	Clopidogrel after Surgery for Coronary Artery Disease
COAST	Heparin-Coated Stents in Small Coronary Arteries
CORONARY	CABG Off or On Pump Revascularization Study
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CREDO	Clopidogrel for the Reduction of Events during Observation
CREDO-Kyoto	Coronary Revascularization Demonstrating Outcome Study-Kyoto
CTSN	Cardiothoracic Surgical Trials Network
CTT	Cholesterol Treatment Trialists
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CVIT-DEFER	Cardiovascular Intervention Therapeutics-DEFER
DEFER	Deferral of Percutaneous Coronary Intervention
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose
ESTABLISH	Demonstration of the Beneficial Effect on Atherosclerotic Lesions by Volumetric Intravascular Ultrasound Analysis during Half a Year after Coronary Event Early Statin Treatment
EVERBIO	Comparison of Everolimus- and Biolimus-Eluting Stents with Everolimus-Eluting Bioresorbable Vascular Scaffold Stents II
EXCEL	Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk
FREEDOM	Future Revascularization Evaluation in Patients with Diabetes Mellitus
GISSI-Prevenzione	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico
GOPCABE	German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IONA	Impact of Nicorandil in Angina
ISAR-SAFE	Intracoronary Stenting and Antithrombotic Regimen-Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting
ITALIC	Is There a Life for DES after Discontinuation of Clopidogrel?
JAPAN-ACS	Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome
JCVSD	Japan Cardiovascular Surgery Database

J-CTO	Multicenter CTO Registry in Japan
JDCS	Japan Diabetes Complication Study
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
JOCRI	Japanese Off-Pump Coronary Revascularization Investigation
J-SAP	Japanese Stable Angina Pectoris Study
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MASS	Medicine, Angioplasty, or Surgery Study
MATRIX	Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angio
NIPPON	Nobori Dual Antiplatelet Therapy as Appropriate Duration
NOBLE	Nordic-Baltic-British Left Main Revascularization Study
OACIS	Osaka Acute Coronary Insufficiency Study
OARS	Optimal Atherectomy Restenosis Study
ORBIT	Oral Glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis
PERFECT	PRE Rapamycin-Eluting Stent FIExi-CuT
PIONEER AF-PCI	Prevention of Bleeding in Patients with AF Undergoing PCI
Post CABG	Post Coronary Artery Bypass Graft Trial
PRECISE-IVUS	Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound
PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients with Atrial Fibrillation versus Long Term Warfarin Therapy
PREVENT	Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial
PREVENT IV	Project of Ex-vivo Vein Graft Engineering via Transfection IV
PROactive	Prospective Pioglitazone Clinical Trial in Macrovascular Events
PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation
RAPCO	Radial Artery Patency and Clinical Outcomes
RAVEL	Randomised Study with the Sirolimus Eluting Bx Velocity Balloon Expandable Stent in the Treatment of Patients with de novo Native Coronary Artery Lesions
ReACT	Randomized Evaluation of Routine Followup Coronary Angiography after Percutaneous Coronary Intervention Trial
REAL-CAD	Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease
RE-DUAL PCI	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
REDUCE	Restenosis Reduction by Cutting Balloon Angioplasty Evaluation
REDUCE-IT	Reduction of Cardiovascular Events with EPA - Intervention Trial
RIVAL	Radial versus Femoral Access for Coronary Angiography and Intervention in Patients with Acute Coronary Syndromes
ROOBY	Randomized On/Off Bypass
SAVE-RITA	Saphenous Vein versus Right Internal Thoracic Artery as a Y-composite trial
SECURITY	Second-Generation Drug-Eluting Stent Implantation Followed by Six- versus Twelve-Month Dual Antiplatelet Therapy
SIRIUS	Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions
SMART	Surgical Management of Arterial Revascularization Therapies
SORT OUT IV	Scandinavian Organization for Randomized Trials with Clinical Outcome IV
SPIRIT	Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Artery Lesions
STARS	Stent Antithrombotic Regimen Study
Steno-2	Intensified Multifactorial Intervention in Patients
With Type 2	Diabetes and Microalbuminuria
STICH	Surgical Treatment for Ischemic Heart Failure
SURVIVE	Surgical Ventricular Reconstruction for Severe Ventricular Dysfunction
SWISSI	Swiss Interventional Study on Silent Ischemia Type
SYNTAX	Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery
TVT	Transcatheter Valve Therapy
WOEST	What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting

Preface to the Revision

The Japanese Circulation Society (JCS) published the "Guidelines for elective percutaneous coronary intervention [PCI] in patients with stable coronary disease" in 2000. In 2006, another guideline titled "Guidelines for the clinical application of bypass grafts and the surgical techniques" was published by the JCS. Because of rapid advances in this field, revision of the guidelines on coronary revascularization techniques (PCI and coronary artery bypass grafting [CABG]) was initiated in 2009. In the review process of the next guideline, rewriting the entire guideline to give comprehensive guidance on coronary artery revascularization was considered. However, the Working Group ultimately decided to develop separate guidelines for revascularization techniques in 2011.

In 2017, the Working Group started drafting a new guideline that incorporates discussion of both PCI and CABG. The decision to create a new guideline was made in recognition that no single treatment technique is appropriate or effective for all patients with coronary artery disease (CAD). Also, a new guideline was needed to incorporate the Heart Team approach that has quickly gained popularity and is becoming recognized as essential for selecting and administering the best care for individual patients. Therefore, this guideline is the first harmonized guideline and the latest revision on standard procedures and recommendations for coronary artery revascularization in 2018.

Five important changes have been made from the previous

guideline and are described below. All of the changes are closely related to how patients with CAD should be treated in the daily clinical setting. The updated guidance is founded on the latest evidence and strongly suggested to be incorporated into CAD care. Note that the scope of this guideline is limited to stable CAD (not acute-phase disease).

1. Optimal medical therapy (OMT) in the general sense (medical therapy combined with lifestyle intervention) can be as effective as coronary artery revascularization in selected patients.
2. Assessment of the functional severity of stenosis (ischemia) is demonstrated to be useful and has made anatomical assessment a dated approach for moderate stenosis. Ischemia-guided care is more desirable than angiography-guided care.
3. Number of involved vessels and SYNTAX score should be used in the complexity assessment of coronary artery lesions.
4. Treatment decision-making based on risk profile is demonstrated to be effective for achieving best results. For the groups of patients described in Class IIb and III recommendations in **Table 13** of **Chapter IV** (see page 493), discussion according to the Heart Team approach is recommended in the treatment decision-making process.
5. Appropriate use of PCI and CABG pursuant to the goal of revascularization is desired.

Although a randomized controlled trial (RCT) may be able to evaluate the true benefit of PCI or CABG, RCT data or meta-analysis alone is insufficient to determine whether PCI or CABG is suitable or to make an accurate prediction of treatment outcomes in individual patients in the clinical setting. Therefore, large-scale multicenter registry data are also important. Although the general conditions, care given, and outcomes of care in Japanese patients with stable CAD are known to show certain differences compared with Europeans or Americans, much of the reliable data come from Europe and the USA. We reference Japanese data as frequently as possible in drafting the guideline to evaluate the extrapolability of European and American data to the Japanese patient population. We must say there are still significant differences in the level of data available. Japanese clinicians and researchers in the field should join forces to generate more quality data that can fill the gap.

We are all aware that standardization of care will soon become the prerequisite for medical care. Performing analyses or preparing guidelines for standardization of care will increasingly require new resources based on different perspectives such as the so-called big data and operation of feedback systems.

The classes of recommendation and levels of evidence used throughout the guideline are summarized in **Tables 1** and **2**, respectively. These are very important to the guideline. Recommendations in the guideline are mostly based on Level A or B evidence.

Table 1. Classes of Recommendation

Class I	Procedure/treatment is supported by strong evidence or widely recognized to be effective/useful
Class II	Efficacy/utility of procedure/treatment is not supported by consistent evidence or widely accepted
Class IIa	Procedure/treatment is likely to be useful/effective based on evidence/opinion
Class IIb	Utility/efficacy of procedure/treatment is not well established by evidence/opinion
Class III	Procedure/treatment is generally viewed, or suggested by evidence, to be not beneficial or even harmful

Table 2. Levels of Evidence

Level A	Multiple randomized clinical trials or meta-analysis
Level B	Single randomized clinical trial or large-scale multicenter registry
Level C	Agreement among experts, small-scale clinical trials or subgroup analyses

I. Diagnosis

1. Symptoms and Signs

Symptoms characteristic of chronic stable angina, a common manifestation of CAD, were first described by William Heberden 250 years ago (feeling of tightness [occasionally with feeling anxious and sweating] induced by exertion, typically under the sternum and precordium with radiating pain in the upper limb, and relieved with rest).[1] Symptoms of exertional angina (or stable angina) are now differentiated by scoring systems (an example is shown in **Table 3**)[2] into typical angina, atypical angina, and noncardiac chest pain. Advances in imaging techniques have revealed some patients have asymptomatic (i.e., no chest symptoms) myocardial ischemia or old myocardial infarction with no clinical manifestations. Some researchers have suggested replacing the term stable angina with a broader term such as stable CAD or stable ischemic heart disease, considering the improved prognosis, achieved largely by medical therapy, for angina pectoris in general.[3,4] For the remainder of this guideline, stable CAD will be used to refer to stable angina (but "stable angina" will be used when citing literature that uses the term).

Estimation of the prevalence of CAD based on coronary risk factors such as age, sex, smoking habit, hypertension, diabetes mellitus (DM), and dyslipidemia is also important for diagnosis. The Framingham Risk Score is a classic algorithm used for that purpose.[5] NIPPON DATA 80[6] and the Suita study[7] are some of the Japanese epidemiological studies similar to the Framingham Heart study that led to the development of the Framingham Risk Score. The "Japan Atherosclerosis Society (JAS) Guidelines for prevention of atherosclerotic cardiovascular diseases 2017" has switched the coronary artery risk calculation chart

Table 3. Chest Pain Score	
Location	
Substernal	+3
Precordial	+2
Neck, jaw, or epigastrium	+1
Apical	−1
Radiation	
Either arm	+2
Shoulder, back, neck, jaw	+1
Character	
Crushing, pressing, squeezing	+3
Heaviness, tightness	+2
Sticking, stabbing, pinprick, catching	−1
Severity	
Severe	+2
Moderate	+1
Influenced by	
Nitroglycerin	+1
Stature	−1
Breathing	−1
Associated symptoms	
Dyspnea	+2
Nausea or vomiting	+2
Diaphoresis	+2
Previous history of exertional angina	+3

Coronary artery disease suspected when the sum of the scores is ≥6. (From Geleijnse ML, et al. 2000.[2] by permission of Oxford University Press (OUP) on behalf of the European Society of Cardiology (ESC). OUP and ESC are not responsible or in any way liable for the accuracy of the translation. The Japanese Circulation Society is solely responsible for the translation in this publication/reprint.)

from that of NIPPON DATA 2017 to that of the Suita study.[8] The risk prediction model based on the Suita study focuses on the strong associations between hypertension and low high-density lipoprotein (HDL) cholesterolemia in males, and between DM and smoking in females with CAD (**Figure 1**).[8,9]

Physical examination often finds no abnormality in patients with stable CAD. Nevertheless, palpation of arteries (primarily the carotid and femoral arteries) to check for bruits is still an essential examination. Measuring Achilles tendon thickness, for example, is important for the detection of familial hypercholesterolemia.[10] Careful auscultation of the heart is also needed to detect extra heart sound such as S4 or a cardiac murmur.

2. Noninvasive Assessment of Ischemia (Table 4)

Exercise ECG is used for detection of ischemia when the patient is able to exercise. However, its sensitivity and specificity are relatively low at approximately 60% and 70%, respectively.[11,12] Instead, a full risk assessment should be conducted using the Duke Score or a similar model. If the patient's risk is moderate or unevaluable, coronary computed tomography angiography (CTA) or exercise single-photon emission computed tomography (SPECT) test[13] is recommended.

When the patient is unable to exercise or ECG is uninterpretable for ischemia assessment for any other reason, coronary CTA, pharmacological stress SPECT or pharmacological stress echocardiography[13] should be chosen. Sensitivity, specificity, and negative predictive value are approximately 85%, 90%, and 83%, respectively.[14] The negative predictive value of coronary CTA increases to 99% in patients with a low pretest probability,[15] making the test suitable for ruling-out CAD. The specificity and accuracy of coronary CTA increase when CT perfusion[16] and CT-derived fractional flow reserve (FFR_{CT})[17] are combined. However, low diagnostic accuracy (46.1%) was reported for the combination of tests in vessels with an FFR_{CT} of 0.7–0.8.[18] The JCS's appropriate use guide on FFR_{CT} specifies that FFR_{CT} is not indicated for (1) patients with stents placed in the left main coronary artery (LMCA) or ≥2 vessels, (2) patients with a history of CABG, and (3) patients with acute myocardial infarction (≤30 days after onset).[19] In patients with chest pain, FFR_{CT} can reduce unnecessary coronary angiography without increasing clinical events[20,21] and is considered a potentially cost-saving approach.[22,23]

SPECT sensitivity and specificity are approximately 73–92% and 63–87%.[24–27] SPECT is preferred in patients with severe coronary artery calcification (calcification score >400), patients with frequent atrial fibrillation (AF) or extrasystoles, and patients in whom the use of contrast media should be avoided (e.g., renal impairment). Perfusion MRI may be an alternative to CT or SPECT.[28]

3. Invasive Assessment of Ischemia (Table 5)

There is some discrepancy between the degree of stenosis on angiogram and the functional severity of the stenosis. For example, reports have noted that angiography can exaggerate the degree of stenosis in the right coronary artery (RCA), left circumflex coronary artery (LCX), or distal artery and may underestimate stenosis severity in the LMCA and lesions around the left anterior descending coronary artery (LAD).[29,30] An FFR measurement becomes useful when an assessment by coronary angiography is not consistent with the results of noninvasive stress test or the clinical presentation (e.g., symptoms). Ischemia assessment using FFR is aimed at evaluating whether coronary artery revascularization should be performed. In other words, FFR-guided revascularization is suitable only for vessels that are anatomically amenable to coronary angioplasty or bypass grafting. For smaller vessels and branches that are not amenable to revascularization, FFR measurement is not indicated.

FFRs of 0.75 and 0.75–0.80 have been frequently reported as, respectively, the threshold value and the area of margin for ischemia in noninvasive stress testing of coronary artery stenosis (exercise ECG, stress echocardiography, stress myocardial scintigraphy).[31,32] At present, an FFR of 0.80 is set as the minimum for the use of new-generation drug-eluting stents (DES), which have improved in their outcomes over the years. Patients, or the lesions assessed to have no ischemia based on FFR, generally have a good prognosis. The DEFER study,[33–35] FAME study,[36–38] and CVIT-DEFER study[39] have shown that stenting in a lesion in which ischemia is not suggested by FFR does not improve survival more than medical therapy alone. For lesions in which the FFR strongly

Sum the scores for individual risk factors [1] through [8] (Score)

[1] Age (years)	
35–44	30
45–54	38
55–64	45
65–69	51
70–	53

[2] Sex	
Male	0
Female	–7

[3] Smoking*	
Smokes	5

[4] Blood pressure*		
Ideal	<120 and <80	–7
Normal	120–129 and/or 80–84	0
Normal high	130–139 and/or 85–89	0
1st degree hypertension	140–159 and/or 90–99	4
2nd degree hypertension	160–179 and/or 100–109	6

[5] HDL-C (mg/dL)	
<40	0
40–59	–5
≥60	–6

[6] LDL-C (mg/dL)	
<100	0
100–139	5
140–159	7
160–179	10
≥180	11

[7] Glucose intolerance	
Yes	5

[8] Family history of premature coronary artery disease	
Yes	5

Sum of [1] through [8] ____

	Sum of [1] through [8]	Probability of occurrence of CAD within 10 years	Range		Median	Risk
			Min.	Max.		
Suita Score (LDL model)	≤35	<1%		1.0%	0.5%	Low risk
	36–40	1%	1.3%	1.9%	1.6%	
	41–45	2%	2.1%	3.1%	2.6%	Medium risk
	46–50	3%	3.4%	5.0%	4.2%	
	51–55	5%	5.0%	8.1%	6.6%	
	56–60	9%	8.9%	13.0%	11.0%	High risk
	61–65	14%	14.0%	20.6%	17.3%	
	66–70	22%	22.4%	26.7%	24.6%	
	≥71	>28%	28.1%		≥28.1%	

Figure 1. Predictive model of coronary artery disease based on Suita score. CAD, coronary artery disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. *No reduction or addition necessary even if the patient is receiving antihypertensive therapy. If the patient's blood pressure remains unchanged with antihypertensive therapy, the patient is at risk of CAD and should be given guidance accordingly. If the patient is working on smoking cessation, consider him/her as not smoking. The risk of coronary artery disease almost halves after 1 year of nonsmoking and equals that of a nonsmoker after 15 years of smoking cessation. (From Kinoshita M, et al. 2018[8] and Japan Atherosclerosis Society 2017.[9] Copyright © 2018 Japan Atherosclerosis Society. This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License. https://creativecommons.org/licenses/by-nc-sa/4.0/)

suggests the presence of ischemia, the FAME 2 study has shown that PCI can reduce the risk of emergency revascularization more than OMT alone.[40,41]

In patients with multivessel disease, although anatomical severity assessment (e.g., number of affected vessels observed on coronary angiography or a SYNTAX score) is useful for prognostic evaluation, angiography tends to exaggerate the degree of stenosis. Only approximately 20% of 3-vessel disease confirmed by coronary angiography is also confirmed by functional assessment of stenosis severity (ischemia).[42] For approximately 40% of patients with multi-vessel disease confirmed by coronary angiography, an FFR measurement can lead to change in treatment strategy.[43,44] When the functional SYNTAX score (SYNTAX score calculated using functional severity of stenosis) is used, approximately 30% of patients who are angiographically

Table 4. Recommendation and Evidence for Noninvasive Techniques for Assessment of Ischemia Prior to Revascularization

	COR	LOE
Detection of ischemia and identification of ischemic lesions using noninvasive techniques (SPECT, stress echocardiography, PET, perfusion MRI) in patients at intermediate risk of coronary artery disease	I	A
Assessment of ischemia in moderate/severe stenosis using coronary FFR_{CT}	IIb	B

COR, class of recommendation; FFR_{CT}, CT-derived fractional flow reserve; LOE, level of evidence; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Table 5. Recommendation and Evidence for Ischemia Assessment Using FFR and iFR

	COR	LOE
PCI in a moderate stenosis that is not the primary lesion and does not reveal ischemia by noninvasive testing in patient with multivessel disease	I	A
Selection of a vessel amenable to PCI in asymptomatic patient	IIa	B
PCI in a moderate to severe stenosis in the LMCA	IIa	B
PCI in multivessel disease	IIa	B
Lesion in a small vessel or branch not amenable to PCI	III	C

COR, class of recommendation; FFR, fractional flow reserve; iFR, instaneous wave-free ratio; LMCA, left main coronary artery; LOE, level of evidence; PCI, percutaneous coronary intervention.

high-risk are reclassified as moderate risk or lower.[45] Because noninvasive imaging tests have limited utility in the evaluation of ischemia in individual lesions in patients with multivessel disease, functional assessment of stenosis with FFR is the more favored approach.

Accurate FFR measurement requires prior caffeine abstinence to ensure maximum blood flow is attained. Intravenous adenosine, intracoronary papaverine hydrochloride, and intracoronary nicorandil are used in FFR measurement. Instaneous wave-free ratio (iFR) is the ratio of the distal and aortic pressure during the wave-free period in which vascular resistance is minimum. Measuring iFR is easy to approach compared with FFR because it does not require maximum blood flow. For PCI, an iFR of 0.89 is used as the treatment threshold and considered to correspond to an FFR of 0.80.[46,47] A recent RCT comparing FFR and iFR has demonstrated that the diagnostic utility of iFR is not inferior to that of FFR.[47,48] Other recently proposed indices that do not require maximum blood flow include diastolic pressure ratio (dPR), diastolic hyperemia-free ratio (DFR), and resting full-cycle ratio (RFR). A strong association has been shown between each of these and FFR, and these indices are suggested to be as clinically useful as iFR. These indices and iFR are now known collectively as resting indices.[49–51] Coronary flow velocity reserve (CFVR) is measured by a Doppler flow wire and is calculated as the ratio of maximum coronary flow velocity at hyperemia to that at rest. CFVR is a diagnostic test for ischemia, reflecting the extent of epicardial coronary artery stenosis and microcirculation, and plays a complementary role to FFR.[52,53]

4. Myocardial Viability

Myocardial viability is commonly assessed by the presence/absence of ischemia and the degree of blood flow reduction using myocardial perfusion SPECT. Thallium 201 (^{201}Tl) evaluates cell membrane and Na/K pump activities, and technetium 99 m (^{99m}Tc) assesses mitochondrial activity.[54] Myocardial perfusion SPECT is considered to have at least equivalent diagnostic sensitivity, but to have lower specificity compared with dobutamine stress echocardiography. The sensitivity and specificity of ^{201}Tl myocardial perfusion SPECT reported in a study were 86% and 59%, respectively.[55] Administering nitroglycerin sublingually is considered effective for avoiding underestimation of myocardial viability in ^{99m}Tc myocardial perfusion SPECT.[56,57] The reported sensitivity and specificity of ^{99m}Tc myocardial perfusion SPECT using nitroglycerin are 81% and 66%, respectively.[58] An uptake ratio (uptake in the affected vs. healthy segment) of ≥50% at rest is an indication of myocardial viability.

When stress myocardial perfusion SPECT fails in complete assessment of myocardial viability, fluorine 18-labeled fluorodeoxyglucose (^{18}F FDG) PET is advised.[59] A "blood flow and glucose metabolism dissociation" suggests myocardial viability (hibernating myocardium). In an observational study of 648 patients with impaired cardiac function (left ventricular ejection fraction [LVEF] 31±12%), survival rate was increased by early revascularization only in patients for whom blood flow and glucose metabolism dissociation had been noted by rest–stress ^{82}Rb/^{18}F FDG PET, with a particularly greater benefit of revascularization observed among patients with >10% viable myocardium.[60]

Gadolinium cannot be used in patients with stage G3b advanced stage chronic kidney disease (CKD); glomerular filtration rate (GFR) <30 mL/min/1.73 m^2. Cardiac MRI with late gadolinium enhancement (LGE) is an alternative technique for myocardial viability assessment in such patients. The myocardium at the site of infarction is considered viable when the proportion of transmural LGE is ≤50%.[61] Even when the wall thickness is <5.5 mm, wall motion can be improved by revascularization if transmural LGE is <50%.[62]

A meta-analysis of 3,088 CAD patients who had impaired cardiac function (LVEF 32±12%) and myocardial viability assessed by SPECT, ^{18}F FDG PET, or dobutamine stress echocardiography reported a survival benefit with revascularization (PCI or CABG) only in patients with myocardial viability.[63] Myocardial viability in patients with impaired cardiac function is therefore of vital importance for determining whether revascularization is indicated, but other information such as patient demographics and disease characteristics also needs to be considered.

II. Treatment Decision-Making by the Heart Team

1. Importance of a Team Approach

In Chapter I of the "Guidelines for elective percutaneous coronary intervention in patients with stable coronary artery disease" (JCS 2011), the importance of collaboration between the cardiologist and cardiac surgeon in the treatment decision-making process is discussed. The guideline also notes that, for a patient with LMCA disease or multivessel disease (particularly those with DM, impaired left ventricular function or valvular disease), the treatment plan should be discussed between the cardiologist and cardiac surgeon before being presented to the patient.

However, discussion between a cardiologist and cardiac surgeon is hardly sufficient for development of a suitable treatment plan for CAD. The new Heart Team approach introduced with transcatheter aortic valve implantation (TAVI) requires rethinking the traditional team approach to CAD therapy.

2. Role of the Heart Team

The foremost responsibility of a Heart Team in the treatment of CAD is to evaluate whether the patient needs coronary artery revascularization, assess whether PCI or CABG is more appropriate for the patient, and present the treatment plan to the patient. In a country with a rapidly aging population, Japanese patients now have more complications with social problems such as isolation of poor, older adults or difficulty of earning. A multidisciplinary Heart Team approach is becoming more relevant to treatment decision-making in today's context.

A holistic approach is expected from the Heart Team when dealing with patients who may have a variety of comorbidities such as valvular disease, impaired cardiac function, renal impairment, DM or systemic vascular disease, rather focusing only on the anatomical complexity of coronary lesions. Expectations for the Heart Team also include assessment of the patient's toleration of antiplatelet therapy, evaluation of the need for continued anticoagulation therapy (considering the risk of AF and venous thrombosis), evaluation of bleeding risk, and assessment of the risk for invasive treatment in the future. The patient's physical, social, and psychological frailty and lifestyle, as well as the patient's/family's preferences, should also be considered in treatment decision-making.

3. Requirements for a Heart Team

The Heart Team must have (1) designated members, (2) a documented treatment decision-making process, and (3) measured treatment outcomes that can be shared among team members. Preferably, the Heart Team should include, rather than be organized as a joint conference of, a cardiovascular interventionist and cardiac surgeon, a general cardiologist, anesthesiologist, expert(s) on comorbidities, and a nurse(s) who is familiar with the patient's performance status as well as the social/family background (**Table 6**).

A fair-minded physician should lead the team and strive to create an atmosphere that encourages input from both physician and non-physician members. Members are expected to build trust and avoid coercive or unfair statements against one another. Active discussion is essential for providing the best care to patients. Team members should be aware of the general team workflow (e.g., what kind of cases the team will cover, how members of different background should engage in treatment decision-making, how the decision-making process is documented, and how the treatment plan chosen by the team is presented to the patient in the informed consent process) (**Table 6**).

The outcome of revascularization, whether PCI or CABG, depends much on the skills of those who perform the procedure and who support it. The skills of team members should therefore be considered during the treatment decision-making process. Measuring (monitoring) the outcomes of care given at the team's institution and sharing statistical analysis of the outcome data among team members allows more informed discussion among members. Registration of treatment outcomes to a nationwide database is essential.

4. Scope of Discussions Within the Heart Team

Ensuring adequate discussion among members with different backgrounds for each and every patient with CAD is difficult and impractical. In fact, the European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines published in 2018 note that, while involvement of a multidisciplinary Heart Team in treatment decision-making is necessary for patients with stable multivessel disease, it is not for stable CAD for which the Heart Team has a pre-established treatment protocol.[64] This guideline lists treatment decision-making by a Heart Team as a Class I recommendation for Class IIb and Class III patients in **Table 13** of **Chapter IV** (see page 493).

Table 6. Typical Members and Activities of a Heart Team

Members
• Interventionist
• Cardiac surgeon
• Cardiologist (team leader) not involved in invasive care
• Anesthesiologist
• Expert(s) on comorbidities
• Ward nurse(s)
• Others as needed
Team activities
- Case conference on a regular basis
- Establishment and agreement on criteria for cases to be discussed at the team conference
- Predetermined agenda and documentation of discussion in the medical record
- Sharing of the outcomes of care given to each patient
- Registration of the outcomes of PCI and CABG to a nationwide database
- Work on improvement of care through team review of mortality and serious morbidity (M&M conference)

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Preferably, an agreed standard treatment plan should be established for cases that are not discussed at the team conference. The Heart Team should also review deaths and serious morbidities that occur after elective intervention. The so-called mortality and morbidity (M&M) conference should be organized with the assistance of the institution to improve care quality.

5. The Heart Team in the Community

PCI may be performed in the cardiology office, and many hospitals with a cardiology department do not have a separate cardiac surgery department even though PCI can be performed. Because of this, close coordination between the cardiologist's office and a hospital with a complete cardiovascular surgery facility is needed. Preferably, the cardiologist who a patient first visits and the hospital that accepts the patient for cardiovascular surgery should assess each other's diagnostic competence and treatment outcome in advance, form a heart team(s) for the community, and organize regular case conference meetings rather than limit their communication to a simple patient referral procedure.

III. OMT

OMT refers to medical therapy alone in a narrow sense. In the broader sense of the term, however, it means medical therapy combined with permanent lifestyle modification through exercise, diet, weight control, and smoking cessation, etc. For treatment of CAD, OMT is more relevant than medical therapy alone. OMT is cost-effective and can also decrease mortality and help alleviate symptoms (**Table 7**).

1. Lifestyle Intervention

1.1 Smoking Cessation

Smoking is associated with increased fibrinogen production,[65] increased platelet aggregability,[66] endothelial dysfunction,[67] low HDL cholesterolemia,[68] and coronary spasm,[69] among others. Smoking is also dose-dependently associated with cardiovascular event risk.[70] Passive smoking also clearly increases the risk of cardiovascular events.[71] Although no RCT data are available about the effects of smoking, a large number of observational studies and meta-analyses have shown that smoking cessation is effective for reducing cardiovascular events.[70,72] Complete cessation of smoking decreases the risk of death and myocardial infarction by 30%[73] compared with continuation of smoking. Even avoiding smoking for 2–3 years can reduce such risks.[74]

There are drug and non-drug treatment strategies to assist smoking cessation. The "5A approach" is a widely accepted program of smoking cessation treatment (**Table 8**).[75] Smoking cessation aids (nicotine patch, nicotine gum, varenicline) can help decrease nicotine dependence. Although smoking cessation aids are clearly effective, there is little evidence about the relationship between them and cardiovascular events.

The physician's encouragement and motivation play an important role in smoking cessation.[76] Physicians should build trust with patients to help them stay away from smoking, not only in workplace but also at home.

Table 7. Recommendation and Evidence for OMT

	COR	LOE
OMT for risk control whether or not revascularization is performed	I	A
Prioritize OMT over revascularization in patients with only a small ischemic area or mild ischemia	I	B

COR, class of recommendation; LOE, level of evidence; OMT, optimal medical therapy.

Table 8. Smoking Cessation: The 5A Approach

Step 1	Ask	Ask about tobacco use each visit
Step 2	Advise	Advise the smoker to quit
Step 3	Assess	Assess willingness to make a quit attempt
Step 4	Assist	Assist in quit attempt. Administer smoking cessation aids and give counseling
Step 5	Arrange	Arrange follow-up

(From U.S. Department of Health and Human Services, Public Health Service. 2008.[75])

1.2 Weight Management

Epidemiological studies have reported an association between body mass index (BMI) and coronary artery events. A meta-analysis has shown that a high BMI is a significant risk factor for coronary artery events even after correction for age, sex, physical activity, and smoking habit, among others.[77] In particular, visceral obesity is known to be a strong risk factor of coronary artery events.[78] Obesity is not only associated with multiple classic coronary risk factors, but also related to increased sympathetic tone, hypercoagulable state, and inflammation, among other things.[79] In Japan, a BMI (calculated as weight in kilograms divided by square of height [in meters]) of 22 is regarded as normal. A person with a BMI ≥25 is regarded as obese, but is considered to be obese only when there are obesity-related health conditions or excess visceral fat.[80] Waist circumference (abdominal circumference) is an important measure of visceral obesity. In Japan, waist circumference is a required criterion for diagnosis of metabolic syndrome[80] Data show that decreasing weight or abdominal circumference can reduce a multitude of risk factors such as blood glucose, blood pressure (BP), and lipid levels.[80] A weight loss of 20–32% achieved by weight reduction surgery reportedly decreased the mortality rate by 24%.[81] For obese patients, a minimum target should be 3% reduction of weight/abdominal circumference in a period of 3–6 months.[80,82]

1.3 Physical Activity and Exercise Therapy

Exercise therapy and cardiac rehabilitation have been shown to be effective in RCTs and meta-analyses,[83] and are the foundation of coronary artery risk management. Exercise therapy can improve the prognosis and also increases exercise tolerance and the ischemic threshold.[84,85] In addition, it is expected to help the patient quit smoking. These benefits of exercise therapy are observed in both acute myocardial infarction and stable CAD.[86] Moderate to intense aerobic exercise for about 30–60 min/day on at least 5 days/week is recommended for most patients.[87] Preferably, the prescription for exercise should be personally created, based on an exercise stress test. A monitored exercise program is recommended for patients with impaired cardiac function, symptoms of heart failure (HF), low exercise tolerance or severe residual ischemia. Together with exercise therapy, the patient should also be encouraged and motivated to increase physical activities in daily life to alter lifestyle habits.

2. Medical Therapy

2.1 Goals

The goals of medical therapy for stable CAD are the improvement of quality of life (QOL) and prognosis through mitigation of ischemia and prevention of cardiovascular events. OMT is shown to improve survival as much as coronary artery revascularization in carefully selected patients with coronary artery stenosis.[35,88–90] Therefore, OMT is integral to the treatment of stable CAD, whether or not the patient undergoes revascularization (see **Chapter IX**, page 538 for antiplatelet drugs and anticoagulants).

However, limited applicability of OMT in the clinical setting has been noted,[91] and continuing efforts to maintain/improve patient adherence to medical therapy is required.

2.2 Antianginal Drugs

2.2.1 Nitrates

Nitrates decrease the preload by dilating peripheral veins, and also lower the afterload by dilating coronary and peripheral arteries. No large-scale RCTs have produced reliable evidence of the efficacy of nitrates in stable CAD. Although one report indicated that nitrates worsen prognosis,[92] the patients were not randomized in an appropriate manner in that study. Further research is needed on the effects of nitrates because of advances in both coronary artery revascularization and medical therapy over the years since the time of that study.

2.2.2 Beta-Blockers (BB)

BB lower myocardial oxygen consumption by lowering both the heart rate (negative chronotropic effect) and myocardial contractile force (negative inotropic effect) to exert an antianginal effect. Reduction of the post-discharge mortality rate was revealed by a meta-analysis of patients given long-term BB therapy after acute myocardial infarction.[93,94] Carvedilol administration lowered arrhythmias and the risk of sudden death after myocardial infarction.[95] However, there is only inconclusive evidence, and research is still ongoing into the effects of BB on survival in stable CAD patients without a history of myocardial infarction or impaired left ventricular systolic function.

2.2.3 Calcium Antagonists

Both dihydropyridines and nondihydropyridines alleviate myocardial ischemia by vasodilatation. A clinical trial indicated that amlodipine decreases cardiovascular events,[96] and long-acting nifedipine reduces the risk of PCI; however, that trial was conducted before the establishment of current revascularization techniques and OMT.[97] Because of the higher prevalence of coronary spasm in Japan compared with Europe and the USA, BB are used less and calcium antagonists are used more frequently.[98]

2.2.4 Nicorandil

Nicorandil is an ATP-sensitive potassium-channel opener developed in Japan. It can alleviate myocardial ischemia and has a myocardial protective effect through its nitrate-like action and coronary vasodilating effect. The IONA study, an RCT conducted early in the first decade of the 21st century (contemporary with calcium antagonists), reported that nicorandil decreased cardiovascular events by 17%.[99]

2.2.5 Other Drugs

Ivabradine (selective sinus node inhibitor) and ranolazine (selective blocker of late Na^+ current) are also clinically used outside Japan. Neither drug had been approved in Japan in 2018.

2.3 Medical Therapy for Coronary Risk Factors

2.3.1 Hypertension

The American Collage of Cardiology (ACC)/American Heart Association (AHA) guidelines on hypertension, published in 2017, state that the target BP for hypertensive patients with chronic CAD should be <130/80 mmHg.[100] The "Guidelines for the management of hypertension 2014" published by the Japanese Society of Hypertension recommend that the target BP should be <140/90 mmHg for patients with CAD, and <130/80 mmHg for patients with multiple risk factors and who have no severe coronary artery stenosis, myocardial ischemia or ECG changes.[101]

For hypertensive patients with chronic CAD, calcium antagonists and BB are the first-line treatments because they have antianginal activity. Calcium antagonists are the first choice in patients suspected to have coronary spasm. Angiotensin converting enzyme inhibitors (ACE-I) improve survival by decreasing cardiovascular complications following myocardial infarction, and have also been shown to improve survival in CAD patients without cardiac dysfunction.[102] The ASCOT[103] and ACCOMPLISH[104] studies reported a reduction in cardiovascular events in patients treated with amlodipine and ACE-I. No reports have demonstrated the utility of angiotensin II receptor antagonists in hypertensive patients with chronic CAD. Aldosterone antagonists, spironolactone and eplerenone, are recommended for myocardial infarction patients who have HF but neither renal impairment nor hyperkalemia.[105,106]

2.3.2 DM

Both the incidence of recurrent cardiovascular events and mortality rate are high in cardiovascular disease patients with DM.[107] In the ACCORD study, however, an increased

mortality rate was observed in the intensive glucose-lowering therapy group,[108] throwing doubt on the utility of rigorous glucose control for suppression of major cardiovascular events. However, starting glucose control early reportedly reduces comorbidities in the long term and also lowers the risk of death (legacy effect). The Japan Diabetes Society's "Diabetes therapy guidelines 2016" sets the HbA1c target for control of complications at <7.0%.[109]

There have been reports of metformin and alpha-glucosidase inhibitors reducing major vascular events in diabetic patients, but the utility of these drugs has not been reported in chronic CAD patients. In the PROactive study, pioglitazone reduced cardiovascular events in a subgroup of patients with a history of myocardial infarction.[110] Pioglitazone, however, has a precaution for edema and also extra care in patients with HF. In the EMPA-REG OUTCOME study that administered the sodium glucose cotransporter 2 inhibitor empagliflozin to diabetic patients, including many with a cardiovascular history, the incidence of the study's composite endpoint was significantly decreased, with a 38% reduction in cardiovascular death.[111] The CANVAS Program study of canagliflozin[112] and the LEADER study of the glucagon-like peptide-1 receptor agonist liraglutide[113] also reported a significant decrease in the respective primary endpoints.

2.3.3 Dyslipidemia

The CTT meta-analysis revealed that a 38.7 mg/dL reduction of low-density lipoprotein (LDL) cholesterol led to a 21% reduction in cardiovascular events.[114] The ESTABLISH study[115] and JAPAN-ACS study[116] in patients with acute coronary syndrome (ACS), as well as the PRECISE-IVUS study in patients with ACS and stable angina,[117] reported that statin trestment alone or with ezetimibe reduced coronary artery plaque. A significant decrease in cardiovascular events was reported with statin + ezetimibe,[118] with statin+proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab in the FOURIER study,[119] and with the PCSK9 inhibitor alirocumab in the ODYSSEY OUTCOMES study.[120] The ESC's guidelines for 2017 on ST-segment elevation acute myocardial infarction states "ezetimibe or PCSK9 inhibitor treatment should be considered when LDL cholesterol remains ≥70 mg/dL after maximum tolerated dose of statin".[121]

The latest "Japan Atherosclerosis Society (JAS) Guidelines for prevention of atherosclerotic cardiovascular diseases 2017" sets the target LDL cholesterol level at <100 mg/dL for prevention of secondary arteriosclerosis or a reduction of ≥50% in patients in whom <100 mg/dL is difficult to achieve. In patients at risk of cardiovascular events (e.g., those with familial hypercholesterolemia, ACS or DM), the Guidelines note "the target LDL cholesterol may instead be <70 mg/dL".[9] The REAL-CAD study in stable CAD reported that the incidence of cardiovascular events in the pitavastatin 4 mg group was 19% lower than in the 1 mg group, and concluded that the maximum dose of statin covered by the National Health Insurance is recommended in Japanese patients with stable angina.[122]

Eicosapentaenoic acid (EPA) administered with statin decreased coronary artery events by 19% in the JELIS study.[123] In the study's analysis of secondary prophylaxis, coronary artery events were reduced by 23% overall, and by 41% in patients with a history of myocardial infarction and PCI.[124] The GISSI-Prevenzione study reported a significant reduction in cardiovascular events with n-3 polyunsaturated fatty acids.[125] A meta-analysis of lipid-lowering therapies indicated only n-3 polyunsaturated fatty acids and statins decrease both cardiac and all-cause mortality rates.[126] However, subsequent clinical trials reported mixed results on the utility of n-3 polyunsaturated fatty acids. The REDUCE-IT study administered high-dose EPA to patients with a cardiovascular history or who were at high risk of cardiovascular disease and had hypertriglyceridemia with well-controlled LDL cholesterol, and they achieved a 25% decrease in the study's primary composite endpoint.[127] Further analysis is necessary for identification of both the patient population that will benefit from high-dose EPA and the adequate dosage.

In the BIP study of patients with either myocardial infarction or stable angina and who had low HDL cholesterolemia, recurrence of myocardial infarction and sudden death were decreased in subjects with triglycerides ≥200 mg/dL and treated with bezafibrate.[128] In the same study, recurrence of myocardial infarction was also decreased in the group of patients with metabolic syndrome.[129] A meta-analysis of the relationship between fibrates and cardiovascular events revealed that fibrates reduce cardiovascular events.[130]

IV. Preparation for Revascularization

1. Outline of Revascularization

1.1 General Guidance for Revascularization

Precautions to be taken when considering revascularization in a patient are summarized below.

1. The lesion(s) must have demonstrated ischemia and be clinically significant.
2. The goal of revascularization (relief of symptoms, improvement of prognosis by reducing cardiovascular event risk, or both) must be defined and shared between the patient and doctor.
3. The patient's risks must be evaluated before revascularization. The risk of the lesion(s) and perioperative risk must be evaluated separately. The SYNTAX score is a reasonable surrogate index for lesion risk (suggests the severity of CAD). SYNTAX score II is a mortality prediction model for the 4-year period after PCI/CABG. Both SYNTAX and SYNTAX II can provide useful information in treatment decision-making. The STS score and JapanSCORE are useful in the assessment of perioperative risk. This Guideline recommends risk evaluation in individual patients using some or all of these indices.
4. The Heart Team should make the treatment decision for severe coronary artery lesions such as LMCA lesion and 3-vessel disease. Ad hoc PCI during coronary angiography of severe coronary artery lesions should be avoided to allow discussion among the Heart Team members first.

Table 9. Severity of Coronary Artery Lesions for Which Revascularization Is Clinically Indicated

For improvement of prognosis
LMCA, >50% stenosis*
Proximal LAD, >50% stenosis*
2-/3-vessel, >50% stenosis*, and LVEF <40%
≥10% ischemic area in left ventricle
Last patent vessel surrounded by multiple occluded vessels, >50% stenosis*
For relief of symptoms
Presence of a significant stenosis* and angina symptoms that interfere with daily activities even on medical therapy

*Ischemia must be documented. LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction. (From Neumann FJ, et al. 2018.[64])

Table 10. Recommendation and Evidence for Risk Evaluation Before Revascularization

		COR	LOE
Surgical risk	JapanSCORE and STS score for prediction of in-hospital mortality rate of coronary artery bypass grafting	IIa	C
Complexity of coronary artery lesions	SYNTAX score for evaluation of complexity of LMCA disease or multivessel lesions	I	B
	SYNTAX score II for treatment decision-making in multivessel disease	IIa	B

COR, class of recommendation; LMCA, left main coronary artery; LOE, level of evidence; STS, Society of Thoracic Surgeons.

1.2 Basis of Revascularization

Revascularization (PCI/CABG), when successful, can alleviate ischemia, reduce clinical manifestations, and improve prognosis (e.g., reduction of risks such as myocardial infarction and death). Such benefits have been established by a number of clinical trials (**Table 9**).[64] In addition to permanent lifestyle modification, medical therapy for CAD is important both for reduction of short-term risks associated with revascularization and for improvement of long-term outcome of revascularization. This Guideline emphasizes that institution of adequate medical therapy prior to revascularization and continuation of medical therapy after revascularization are both very important. In other words, revascularization and medical therapy complement each other for the treatment of CAD.

RCTs have reported that many patients benefit more from revascularization than medical therapy alone,[131–133] but there are many limitations to realizing similar results in the clinical setting. For example, in the RCTs revascularization is usually performed only on relatively young patients who have normal left ventricular function and no history of revascularization. Also, even when assigned to medical therapy alone, patients in an RCT may undergo revascularization when needed. In other words, no pure comparison between revascularization and medical therapy is feasible in a clinical trial. Also, many old RCTs performed revascularization under angiographic guidance and were not required to demonstrate ischemia using fractional flow reserve (FFR) or iFR. More recent RCTs have shown ischemia-guided revascularization has more benefits than angiography-guided revascularization.[37,39,134] It is now widely accepted that a 75% stenosis on angiography does not necessarily indicate ischemia.[29,30] The severity of a coronary artery lesion can generally be assessed on coronary computed tomography or angiography images. However, a moderate stenosis requires use of another modality to determine if the lesion is actually causing ischemia. The area of ischemia, if determined, provides important information for deciding whether revascularization should be performed. Finally, the follow-up period in many RCTs is generally too short to accurately assess the benefits of CABG with arterial graft.[135–138]

Revascularization is justified only when the expected benefits outweigh the risks involved. Prior risk evaluation and Heart Team discussion are important for justification of revascularization in the clinical setting.

2. Risk Prediction Models (Table 10)

The expected benefits of revascularization therapy must outweigh the risks involved. Medical therapy, PCI or CABG should therefore be chosen based on their benefit-to-risk ratios. Choice of a risk prediction model to be applied for evaluation of both benefits and risks is therefore very important for treatment decision-making.

2.1 Risk Prediction Models for PCI

Risk prediction models are divided into those suitable for prediction of short-term prognosis and those for prediction of medium-to-long-term prognosis. Common models are listed in **Table 11**.[139] Short-term (30 days) models include STS score and European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, among others, but their utility for prediction of short-term prognosis after PCI has not been established. This is because of the marked improvement in short-term PCI outcomes in recent years. Medium-to-long-term prediction models are more suited for assessment of prognosis after PCI. This contrasts with CABG for which reduction of perioperative risk is more important than improvement of long-term outcome.

2.1.1 Risk Prediction Using Coronary Angiography

Because the number of involved vessels affects the natural history of CAD, it has been used in risk stratification. This is the simplest model and does not reflect the size of territories affected. The jeopardy score was developed to roughly calculate the area of ischemia caused by each lesion. The jeopardy score categorizes the degree of stenosis in each lesion into 6 levels (≤25%, 25%, 50%, 75%, 95%, and 100%), groups coronary arteries into 6 segments (**Figure 2**),[140] and assigns 2 points per ≥75% stenosis in each segment for calculation of the total score. Although the jeopardy score is a simple tool, it enables more accurate severity evaluation of coronary artery lesions compared with simply counting the number of involved vessels and is shown to have prognostic value.[140]

More recent models that utilize coronary angiography include the British Cardiovascular Intervention Society myocardial jeopardy score (BCIS-JS), which combines the jeopardy score with scores for LMCA lesions and bypass graft lesions,[141] and the SYNTAX score that incorporates the morphology of vascular lesions.

Table 11. Risk Prediction Models for Revascularization

Model		Procedure	Outcome	Utility for CABG	Utility for PCI
Short-term models	STS	100% CABG	Hospitalization or 30-day mortality, and in-hospital morbidity	◎	
	EuroSCORE II	47% CABG	In-hospital mortality	○	△
	NCDR CathPCI	100% PCI	In-hospital mortality		△
	EuroSCORE	64% CABG	Operative mortality	×	×
	JapanSCORE	100% CABG	Operative mortality	◎	
Medium–long-term models	SYNTAX		MACCE	○	◎
	SYNTAX II	50% CABG	4-year mortality	○	○
	ASCERT CABG	100% CABG	Mortality after >2 years	○	
	ASCERT PCI	100% PCI	Mortality after >1 year		○
	Logistic Clinical SYNTAX	100% PCI	1-year MACE and mortality		○

◎=very useful, ○=useful, △=limited utility, ×=not useful at all. CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MACE, major adverse cardiovascular event; MACCE, major adverse cardiac or cerebrovascular event; NCDR, The National Cardiovascular Data Registry (NCDR®); PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons. (From Windecker S, et al. 2014.[139])

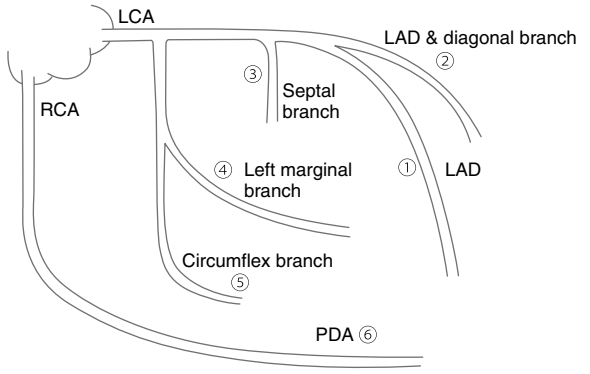


Figure 2. Diagram of coronary artery tree demonstrating 6 segments counted in jeopardy score. LAD, left anterior descending coronary artery; LCA, left coronary artery; PDA, posterior descending artery; RCA, right coronary artery. (From Califf RM, et al. 1985.[140] Copyright (1985) by the American College of Cardiology Foundation, with permission from Elsevier. https://www.sciencedirect.com/journal/journal-of-the-american-college-of-cardiology.)

Table 12. Groups of Risk Prediction Models for Revascularization

Anatomic features
- SYNTAX score
- MSCT SYNTAX score

Anatomic features + clinical evaluation
- Global Risk Classification
- Clinical SYNTAX score
- Logistic Clinical SYNTAX score
- SYNTAX score II

Functional severity of stenosis (ischemia)
- Functional SYNTAX score

Postoperative assessment
- Residual SYNTAX score
- CABG SYNTAX score

CABG, coronary artery bypass grafting; MSCT, multi-slice computed tomography.

2.1.2 SYNTAX Score

The SYNTAX score is currently the most popular risk prediction model. It involves evaluation of coronary artery dominance, the site of lesions, and lesion morphology. All lesions in vessels ≥2 mm in diameter with ≥50% stenosis are subject to evaluation under the SYNTAX score. The score adapted an older evaluation technique based on angiography and its scoring system is based on expert consensus rather than rigorous statistical analysis. The SYNTAX score became widely known after the SYNTAX study reported its utility for stratification of prognosis after PCI.[142,143] A number of studies after the SYNTAX study have confirmed the clinical utility of the SYNTAX score for prediction of risks after PCI in 3-vessel disease or LMCA. SYNTAX scores of ≤22, 23–32, and ≥33 are respectively grouped as low, moderate, and high risk. The SYNTAX score does not have strong relevance for perioperative or long-term outcome of CABG.[144]

2.1.3 Models Combining Anatomic and Demographic Variables

The SYNTAX score represents the anatomic features (complexity and extent) of lesions. Although it is useful for risk prediction, the patient's long-term prognosis is not solely determined by the severity of CAD. For instance, patient demographics are important determinants. There are a few models combining the SYNTAX score with patient demographic variables (**Table 12**).

The SYNTAX score II is one such model (**Figure 3**). It combines the SYNTAX score with demographic and other patient characteristics (age, creatinine [Cr] clearance, LVEF, unprotected LMCA lesion, occlusive peripheral

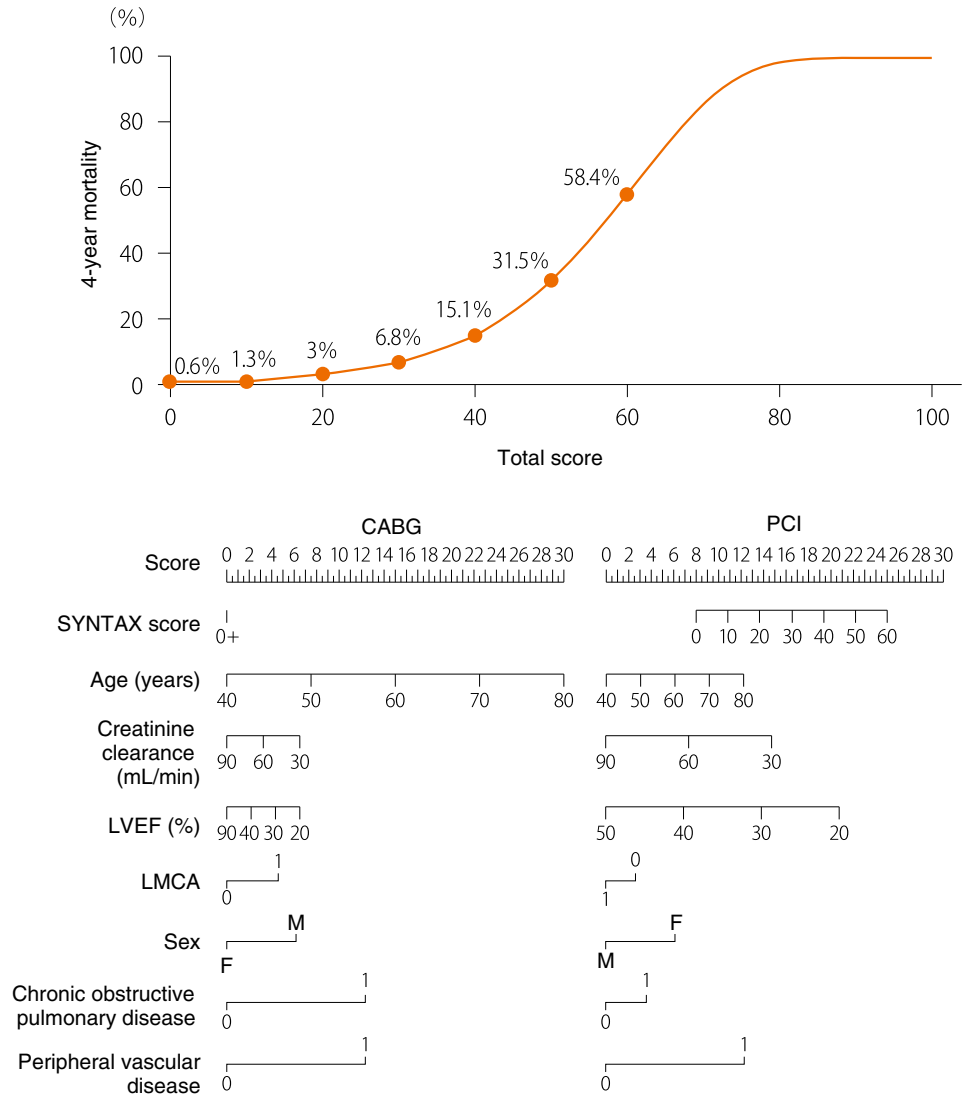


Figure 3. SYNTAX Score II. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction. (From Farooq V, et al. 2013.[145] Copyright (2013), with permission from Elsevier. https://www.thelancet.com/journals/lancet/.)

arterial disease [PAD], sex, and chronic obstructive pulmonary disease).[145] Its utility has been demonstrated in both PCI and CABG patients.[146–149] The EXCEL study was a comparative study assigning patients with LMCA lesions to CABG or PCI based on their SYNATX score II. The 4-year survival predictions by SYNATX score II were accurate for both CABG and PCI.[146] The study also reported that survival outcomes were better than the predictions in patients who were elderly males with chronic obstructive pulmonary disease and underwent PCI, and also in young females who had renal impairment and impaired left ventricular function and underwent CABG.[146]

The CREDO-Kyoto PCI/CABG Registry Cohort-2 was a Japanese study conducted using the SYNTAX score II. The study reported, based on analysis of 2,190 PCI patients and 1,796 CABG patients, that the SYNTAX score II was useful for predicting long-term outcomes of both PCI and CABG, and was more useful than the SYNTAX score for risk stratification.[147] Although further analysis is required, the SYNTAX score II is considered to be more clinically relevant and useful for treatment decision-making than the SYNTAX score because it enables prediction of 4-year survival for both CABG and PCI.

2.1.4 Summary

There are a number of risk prediction models, but few studies have compared one model against another. Also, no model has so far incorporated frailty, which is expected to gain importance in the aging population, or is ready for risk prediction in patients with a porcelain aorta. Also, no single model is capable of assessing both the short-term benefits of PCI and the long-term benefits of CABG. None of the risk prediction models is intended for QOL prediction, either.

2.2 Risk Prediction Models for CABG

Risk prediction models for surgical coronary artery revascularization have been used for many years, primarily in Europe and the USA. The Parsonnet score is one of the oldest models.[150] The simpler and more accurate EuroSCORE was developed and quickly gained popularity globally,[151] partly because it was published on the Internet.[152] Comparison between the Parsonnet score and EuroSCORE started soon after, and the Parsonnet score lost favor.

In North America, the Society of Thoracic Surgeons (STS) led the foundation of the STS National Cardiac Database to accumulate useful data for development of a new model.[153] Thanks to the vast number of CABGs performed in North America, new models were developed, with publication of a new risk score after a few years.[154] The STS update the risk models regularly, which is available on the STS website.[155] The STS have developed a new model for CABG+valve replacement (primarily aortic valve) in addition to the one for CABG alone.[156] In 2018, the STS expanded application of the models to other cardiovascular surgeries using newly accumulated data.[157,158]

In Europe, the simple EuroSCORE was soon accepted and widely used. The more accurate EuroSCORE II was published in 2012.[159] It was developed from data collected from 22,381 patients at 154 facilities in 43 countries. Because the data were collected in a relatively short period (12 weeks from May through July 2010), some researchers have noted that it may be biased.[160] Nevertheless, the EuroSCORE II is simple to use and used globally, including in Japan.[152]

In Japan, development of the nationwide Japan Cardiovascular Surgery Database (JCVSD) started in 2000. The momentum to develop a database started at the Asian Society for Cardiovascular and Thoracic Surgery (ASCVTS) conference in 1999. At that meeting, participants agreed that a new Asian model was needed in light of the STS risk models in the USA, and the EuroSCORE in Europe. Because collecting data from different countries in Asia simultaneously was thought to be unrealistic, a Japanese database was conceived as a pilot case. Data collection first started with 5 institutions in Japan. The data items and their definitions were borrowed from the STS database (with STS approval and cooperation). In 2004, a web entry system, which was technically advanced at the time, was introduced for data collection, and the number of participating institutions gradually increased.[161] An original risk model was completed in 2008, and the original Japanese risk score, JapanSCORE, was published.[162] An updated risk model was made available in 2011,[163] together with a new and more accurate risk scoring system, JapanSCORE II. A smartphone application (for iOS and Android) for convenient patient assessment was introduced in 2018 and is well accepted by the clinical community.

Risk scoring systems developed in the EU/USA use information collected from patients in their countries. Because differences in national healthcare systems certainly affect risk evaluation, one risk scoring system may not be equally relevant in the different countries. A comparison between the STS risk scoring system and EuroSCORE was conducted soon after their development.[164] Accuracy variance of the risk scoring systems in different countries seems inevitable.[165] A meta-analysis comparing the STS, EuroSCORE II, and ACEF (Age, Creatinine, Ejection Fraction) scores reported that STS and EuroSCORE II are superior to the ACEF score without a significant difference between STS and EuroSCORE II.[166] However, the STS risk scoring system is apparently more reliable, because it continues to be updated frequently compared with EuroSCORE II, which has remained unchanged.

Because JapanSCORE is an original system based on Japanese patient information, it is expected to be more relevant to the Japanese population than systems developed elsewhere. Kurazumi et al compared JapanSCORE with EuroSCORE using data obtained from 523 patients treated at their hospital. They reported that the overall c-coefficient under the receiver operating characteristic (ROC) curve was 0.688 for the Logistic EuroSCORE and 0.770 for JapanSCORE. For isolated CABG alone, it was respectively 0.564 and 0.790, revealing the superiority of JapanSCORE with a statistically significant difference (P=0.001).[167] Umehara et al performed a similar comparison using data from 733 patients at their hospital, and reported that the c-coefficient was 0.740 for the Logistic EuroSCORE and 0.806 for JapanSCORE.[168] These findings support the use of JapanSCORE for Japanese patients in the clinical setting.

Because cardiovascular surgeries are performed daily and constantly evolving, databases also require frequent updates. Databases should be continually expanded and refined to maintain/improve their relevance.

3. Location of Lesions, Number of Involved Vessels, and Treatment Decision-Making

3.1 Input Into Treatment Planning

Treatment outcomes of CAD have been improved by technical advances such as DES, OMT, internal thoracic artery (ITA) graft use, and off-pump coronary artery bypass (OPCAB).[169] The benefits of each new treatment technique compared with older techniques have been investigated in clinical trials. Risk prediction models and the treatment decision-making process have also changed significantly over time. In general, a guideline is thought to cover only 20–30% of the entire patient population. In the USA, "appropriate use criteria" (AUC) have been developed to support the rational use of coronary revascularization in different clinical scenarios.

We also aim to present this guideline as practical and relevant guidance for appropriate use of revascularization in Japan based on latest evidence. In fact, the COR and LOE shown in **Table 13** for PCI and CABG for different types of coronary artery lesions are similar to the AUC published in the USA in 2017. For example, the COR for PCI in the proximal LAD artery is IIa. Although recent evidence outside registries is lacking, PCI in the proximal LAD is generally regarded as beneficial and commonly performed in the clinical setting. The AUC updated in 2017 also states that PCI in proximal LAD is "appropriate".[170] For 1-vessel disease other than in the proximal LAD, however, there are large differences between the Japanese and American clinical communities about appropriate treatment. Because PCI for 1-vessel disease (other than in the proximal LAD) is supported by the results of the J-SAP study and is common practice in Japan, this guideline recommends the procedure as Class I.

Other points to note in **Table 13** are severity evaluation, DM, and the Heart Team.

Table 13. Recommendation and Evidence for Revascularization in Stable Coronary Disease

			PCI		CABG	
			COR	LOE	COR	LOE
Heart team conference for cases of COR IIb and III			I	C	I	C
Risk prediction (SYNTAX score, STS risk models, JapanSCORE)			I	B	I	B
ad hoc PCI			IIb	C	–	–
1-vessel disease	No proximal LAD lesion		I	C	IIb	B
	Has a proximal LAD lesion		IIa	C	I	C
2-/3-vessel disease without DM	SYNTAX score ≤22		I	B	I	A
	SYNTAX score 23–32		IIa	B	I	A
	SYNTAX score ≥33		III	B	I	A
2-/3-vessel disease with DM	SYNTAX score ≤22		IIa	B	I	A
	SYNTAX score 23–32		IIb	B	I	A
	SYNTAX score ≥33		III	B	I	A
Unprotected LMCA lesion	SYNTAX score ≤22	Bifurcation lesion not requiring 2 stents	I	B	I	A
		Bifurcation lesion requiring 2 stents	IIb	B		
	SYNTAX score 23–32	Bifurcation lesion not requiring 2 stents	IIa	B	I	A
		Bifurcation lesion requiring 2 stents	IIb	B		
	SYNTAX score ≥33		III	B	I	A
Impaired cardiac function (LVEF <35%)			IIb	C	I	B

CABG, coronary artery bypass grafting; COR, class of recommendation; DM, diabetes mellitus; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LOE, level of evidence; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

Available data consistently indicate that severity evaluation of coronary artery lesions is the key factor in treatment decision-making. In the past, the severity of a coronary artery lesion was evaluated solely by the number of involved vessels. Many past guidelines adopted the same approach to severity assessment. The SYNTAX score then incorporated the location and morphology of lesions into risk prediction and soon was recognized as the most robust model for severity evaluation.[142–144]

The SYNTAX score for severity evaluation in multivessel disease and LMCA lesions is endorsed in this guideline.

For a single LMCA lesion requiring 2 stents, however, COR IIb is assigned irrespective of the SYNTAX score, because although the outcomes of PCI in LMCA lesions have improved dramatically over the years, risks (secondary revascularization, death, and thrombosis) are still relatively high for patients who require 2 stents compared with those who need only 1 stent.[171]

Another important factor that affects treatment planning is DM. A number of clinical trials have demonstrated the superior benefits of CABG compared with PCI in patients with DM.[144,172] However, the relationship between the baseline SYNTAX score and the outcome of PCI/CABG was not studied for a long time. In 2018, a pooled analysis of data from 11,518 patients with multivessel disease or LMCA lesions in 11 comparative studies was published.[173] The analysis revealed that 5-year survival rate was similar between CABG and PCI in nondiabetic patients with multivessel disease, but was higher with a statistically significant difference for CABG among DM patients. The observed difference was more notable in patients with more complex lesions.[173] Although no similar meta-analyses are available, the pooled analysis included a large dataset including data from most of the major and well-respected clinical trials. We therefore decided to incorporate the finding reported by the analysis into this guideline.

The recommendations shown in **Table 13** include stratification by combining DM and severity of CAD. Better outcomes of both CABG and PCI in diabetic patients have been reported in Japan compared with the USA.[174,175] However, no reliable data are available on the outcomes of PCI/CABG in diabetic patients having lesions with a low SYNTAX score. Collection of such data is eagerly awaited.

The advent of 2nd-generation DES has narrowed the variability in PCI outcomes. Recent studies show that the outcomes of PCI are almost equal those of CABG.

However, patients treated in clinical trials share relatively similar backgrounds compared with the general patient population. Also, treatment plans in the clinical setting are not decided solely on the location or morphology of lesions. For instance, CABG is superior to PCI for complete revascularization of complex multivessel disease and also for improvement of survival. Less invasive PCI has greater advantage, however, in elderly (≥80 years) patients in whom angina control is the primary goal.

Treatment for a patient should be decided in consideration of its goal, potential risks of different treatments, physician's skills, and patient preferences, among others. Evaluating risks other than those of CAD is therefore necessary. Because available evidence is insufficient for lesions with COR IIb or III in **Table 13**, the Heart Team should engage in an open discussion during the treatment decision-making process, reviewing data available at their institution or in their community.

3.2 Single-Vessel Disease

Single-vessel disease is grouped into proximal LAD lesions and lesions in other areas.

Proximal LAD lesions are high-risk disease and closely associated with survival. CABG with ITA grafts or PCI with new-generation DES is indicated for these lesions. Classic meta-analyses indicate the long-term outcomes (mortality rate and incidence of myocardial infarction/stroke) of PCI are similar to those of CABG, but the repeat revascularization rate is higher for PCI.[176,177] However, those meta-analyses included data from clinical trials that only used bare-metal stent (BMS) in PCI. Due to the dramatic decrease of repeat revascularization with DES,[178] a similar analysis today is expected to produce a much different result. The j-Cypher Registry, a prospective study of sirolimus-eluting stents (SES), compared the outcomes of revascularization of ostial LAD lesions in 481 patients and of non-ostial proximal LAD lesions in 5,369 patients, reporting little difference in the 3-year repeat revascularization rate or the incidence of myocardial infarction/death.[179] The New York State registry compared the outcomes of CABG and PCI in isolated LAD lesions in propensity-matched patients (n=715 each) and reported no difference in 3-year survival.[180] These reports indicate that the outcomes of PCI with DES placement in ostial LAD lesions is comparable, unlike in non-ostial LAD lesions, to those of CABG and that PCI is a viable alternative to CABG for ostial LAD lesions.

For total ostial occlusion or ostial LAD lesions with complex morphology, however, long-term survival is the primary concern and CABG is still the preferred procedure.

Evidence showing the benefits of revascularization in 1-vessel disease other than in the proximal LAD is lacking. Because of this, recommendations given by non-Japanese guidelines vary widely. The ACC/AHA guideline published in 2012 classifies both PCI and CABG as Class III in terms of prognosis.[181] The weak recommendation reflects the lack of evidence showing the superiority of PCI over medical therapy.[88,89] The ESC/EACTS guidelines of the year 2018 give Class I and IIb recommendations for PCI and CABG, respectivey.[64] Studies comparing ischemia-guided PCI and medical therapy have consistently reported the greater benefit of PCI.[36,40] A meta-analysis of data from 3 comparative studies that give ischemia-related data (subgroup analysis in the COURAGE, FAME2, and SWISSI studies) indicated PCI decreases the 3-year mortality rate more than medical therapy.[182]

This guideline uses the same COR as in the 2018 ESC/EACTS guideline. However, the following points noted by the AUC as the key factors for treatment planning are supported: (1) presence/absence and extent of ischemia, (2) with/without prognostic determinants such as HF, (3) severity of angina symptoms, and (4) medical therapy regimen.[170] Although not empirically well supported, proximal LCX disease in patients with left-dominant coronary circulation is considered to be clinically equivalent to a proximal LAD lesion.[170]

3.3 Multivessel Disease

The BARI 2D and FREEDOM studies investigated multivessel disease in DM patients.[172,183] The BARI 2D study compared revascularization (CABG or PCI) with medical therapy alone against OMT and reported that only CABG achieved a lower incidence of cardiac death and myocardial infarction compared with medical therapy alone.[183] The FREEDOM study assigned 1,900 patients to CABG or PCI and compared outcomes. Both the 5-year mortality rate and the incidence of myocardial infarction in the CABG group were lower, with a statistically significant difference, than in the PCI group (mortality, 10.9% vs. 16.3%; myocardial infarction, 6.0% vs. 13.9%), and the incidence of stroke was significantly higher in the CABG group (5.2% vs. 2.4%).

The SYNTAX study revealed the significance of rating the complexity of CAD. The 5-year all-cause mortality, incidence of myocardial infarction, and repeat revascularization rate in the GABG group vs. PCI group were, respectively, 9.2% vs. 14.6%, 3.3% vs. 10.6%, and 12.6% vs. 25.4%, revealing the superiority of CABG with a statistically significant difference in each endpoint (respectively P=0.006, 0.001, and 0.001). Subgroup analysis using the SYNTAX score showed little difference in the composite endpoint (all-cause death, myocardial infarction, repeat revascularization) between CABG and PCI (26.8% vs. 33.3%, P=0.21) among patients with a low score (0–22), but the incidence of the composite endpoint was lower with a statistically significant difference in the CABG group among patients with medium (23–32) and high (≥33) scores (respectively 22.6% vs. 37.9%, P=0.0008; 24.1% vs. 41.9%, P=0.0005).[143]

Subsequent clinical trials have reported similar results to those of the SYNTAX study. For example, the BEST study assigned 880 patients to PCI with 2nd-generation DES or to CABG and reported little difference in mortality rate over a follow-up of 4.6 years, but with a statistically higher incidence of myocardial infarction and repeat revascularization in the PCI group than in the CABG group.[142] A pooled analysis of 5,054 patients with 3-vessel disease from 11 comparative trials revealed no difference in outcome between CABG and PCI in non-DM patients, but found a lower 5-year mortality rate for CABG in DM patients, with a greater difference in patients with higher SYNTAX scores.[173]

The CREDO-Kyoto registry was a post-hoc analysis comparing the outcomes of CABG and PCI in 5,651 cases of 3-vessel disease. Although CABG was found to be associated with an increased stroke risk, it also correlated with a lower overall risk of death.[184] The CREDO-Kyoto registry compared the above data with contemporary

American registry data and noted differences in the outcomes of revascularization between Japanese and American DM patients.[174]

From the New York State registry, a comparison between CABG against PCI with 1st-generation DES, and another between PCI with 2nd-generation DES and synchronous CABG have been reported.[137,185] The comparison of 17,400 cases between 2003 and 2004 revealed a statistically higher 18 months survival rate in the CABG group.[137] However, the 2015 report noted little difference in mortality (2.8-year mean follow-up; 3.1% per year for PCI and 2.9% per year for CABG; P=0.50). Nevertheless, the PCI group had a higher incidence of myocardial infarction (1.9% per year vs. 1.1% per year, P<0.001) and repeat revascularization rate (7.2% per year vs. 3.1% per year, P<0.001). In contrast, stroke incidence was significantly higher for CABG (0.7% per year vs. 1.0% per year, P<0.001).[185]

As these reports show, the treatment outcomes of multivessel disease depend on the complexity of disease and patients with or without DM. In general, the more complex a lesion in a DM patient, the greater the benefits of CABG compared with PCI. In this guideline, recommendations are stratified by combining DM and the severity of CAD.

3.4 LMCA Disease

Since the establishment of CABG's superiority to medical therapy in clinical trials in 1980s,[186–188] CABG was long considered to be the absolute indication for revascularization in LMCA disease. PCI used to be associated with a high late restenosis rate. Also, many patients with LMCA disease also have multivessel disease for which CABG has better survival benefit, making PCI traditionally the less favored technique.[189,190] However, recent reports indicate that PCI with DES in selected patients is similar in outcomes to CABG for up to 5 years.[142,191,192]

The SYNTAX study compared CABG and PCI in 705 patients with LMCA lesions and reported no significant differences in 5-year survival (14.6% for CABG and 12.8% for PCI; P=0.53), incidence of myocardial infarction (respectively 4.8% and 8.2%; P=0.10), and incidence of the composite endpoint (death, myocardial infarction, stroke, and repeat revascularization: 31.0% and 36.9%; P=0.12). At the same time, however, the study revealed a significantly higher incidence of stroke for CABG, and a significantly higher repeat revascularization rate for PCI.[142,192] Subgroup analysis of the SYNTAX study also indicated that the incidence of the composite endpoint varied among patients with different SYNTAX scores. The incidence of the composite endpoint was similar between CABG and PCI in low-risk (SYNTAX score 0–22) and medium-risk (23–32) patients (P=0.74 and P=0.88, respectively), but was significantly higher in the PCI group among high-risk (≥33) patients (P=0.003).[192] This particular finding from the subgroup analysis suggests that PCI is reasonable for patients with a SYNTAX score ≤32.

The more recent EXCEL study produced similar results. It assigned 1,905 LMCA disease patients with a SYNTAX score ≤32 to either CABG or to PCI with 2nd-generation DES and followed the patients for 3 years after revascularization. The incidence of the composite endpoint (all-cause death, myocardial infarction, and stroke) was 15.4% for PCI and 14.7% for CABG, demonstrating the noninferiority of PCI.[193] The noninferiority of PCI was consistently observed, with no interaction with risk factors such as DM, CKD, and bifurcation lesion.[193] The NOBLE study assigned 1,201 patients to either PCI with early, thick-strut DES or to CABG and compared the 5-year major adverse cardiac or cerebrovascular event (MACCE) rate. The noninferiority of PCI to CABG was hypothesized, but was not achieved, with the 5-year MACCE rates of 29% vs. 19% (P=0.0066). The study report noted that the exclusion of perioperative myocardial infarction, the higher incidence of stent thrombosis (ST) compared with previous reports in the PCI group (despite similar mortality rates), and the higher incidence of late stroke in the PCI group were reasons for the hypothesis not being achieved.[194]

None of the meta-analyses of these RCTs comparing PCI with DES against CABG revealed a difference in 5-year survival or the incidence of myocardial infarction.[195–198] Also, a pooled analysis of 4,478 cases reported little difference between CABG and PCI in DM patients.[173]

Therefore, PCI is a potential alternative to CABG in revascularization of LMCA disease. However, variability of outcomes has been noted in patients with different SYNTAX scores.[198] PCI is reportedly safer in the short term, whereas CABG is supported for better long-term safety due to the higher risk of repeat revascularization associated with PCI. Longer follow-up data are needed to make a more complete comparison.

A Japanese report noted that 5-year outcomes of 1-stent PCI are similar between LMCA bifurcation lesions and nonbifurcation LMCA lesions and that, with 2-stent PCI, the risk of death (including repeat revascularization) and thrombosis is slightly higher for LMCA bifurcation lesions despite no difference in mortality.[171] Although outcomes of PCI are probably similar to those of CABG in most bifurcation lesions, no sweeping generalization can be made for all types of LMCA disease. In this guideline, the COR for PCI in bifurcation lesions that require 2 stents is IIb regardless of the patient's SYNTAX score, but only after discussion within the Heart Team. For PCI in complex lesions, operator skills/experience and patient demographic and baseline characteristics must always be considered.

3.5 Complete Revascularization (Table 14)

Complete revascularization is normally confirmed by diagnostic angiography. It is defined as successful treatment of any lesion with >50% diameter stenosis in vessels ≥1.5 mm, regardless of the size of the territories the vessel is supplying.[199] The effects of complete and incomplete revascularization on patient prognosis have been investigated based on this definition.

Poorer long-term outcomes have been reported for both PCI/CABG with incomplete revascularization.[199,200] There are other contradictory reports. One report noted that outcomes of PCI were less favorable with incomplete revascularization, while those of CABG were similar between complete and incomplete revascularization.[201] Another report concluded that outcomes of both PCI and CABG were similar with or without complete revascularization.[202] Only incomplete revascularization is attained in CABG; most notably, when the target artery is small or has diffuse disease. In PCI, incomplete revascularization has the same causes. At the same time, incomplete revascularization is selected in lesions with complex morphology or in other lesions that are technically difficult to intervene for other reasons (e.g., total occlusion, severe calcification). Incomplete revascularization of a proximal lesion by PCI

Table 14. Recommendation and Evidence for Complete Revascularization

	COR	LOE
Multivessel disease	I	A
Prior functional assessment of severity (ischemia)	IIa	B

COR, class of recommendation; LOE, level of evidence.

Table 15. Prerequisites for Ad hoc PCI

1. Ischemia is documented.
2. The Heart Team has decided that PCI is anatomically feasible and safe.
3. The patient is fully informed.

PCI, percutaneous coronary intervention.

tends to leave clinically relevant distal segments with insufficient flow.

To improve the prognosis for multivessel disease, complete revascularization is desirable. However, deciding whether complete revascularization is appropriate is difficult based solely on anatomic variables such as vessel diameter. A revascularization technique must always be chosen by considering the effect of the size of the territory to which blood is supplied by the treated vessel and the viable myocardial mass on prognosis after revascularization. Revascularization guided by FFR has been reported to improve graft patency.[203] Complete revascularization guided by ischemia may improve long-term outcomes of both PCI and CABG. Fundamentally, however, either complete or incomplete revascularization should be chosen depending on the treatment goal for each patient.

4. Timing of Revascularization and Ad hoc PCI

Delayed intervention can increase the risk of events such as myocardial infarction. Revascularization, once decided, should therefore be done within a reasonable timeframe for the patient's safety.[204–206] The ESC/EACTS guidelines of 2018 recommend that revascularization be carried out within 2 weeks in patients with LMCA disease or severe cases with frequent anginal episodes even on oral antianginal therapy, or within 6 weeks in other stable angina patients for whom revascularization is indicated.[64]

4.1 Ad hoc PCI

Because coronary CT angiography enables physicians to evaluate CAD before intervention, ad hoc PCI in which PCI is performed immediately after coronary angiography reveals CAD has become an accepted treatment approach. Ad hoc PCI is time- and cost-efficient and may also mean less stress to the patient. According to an analysis of CREDO-Kyoto Cohort 2, adjusted 5-year survival rate was no different between 1,722 (24.8%) patients with ad hoc PCI and 5,221 (75.1%) patients without ad hoc PCI (15% vs. 15%, P=0.53), with even a slightly lower incidence of stroke in patients with ad hoc PCI (hazard ratio [HR], 0.78; P=0.06).[207] Despite the benefits, concerns have been raised that ad hoc PCI tends to be performed even when it is not clearly needed/appropriate. ad hoc PCI also tends to be performed without adequate informed consent. In this guideline, 3 prerequisites for ad hoc PCI (**Table 15**) are defined, and routine performance of the procedure is not endorsed.

4.2 Multistage PCI vs. One-Stage PCI for Multi-Vessel CAD

Staged PCI is a common approach for the treatment of multivessel disease. Dividing PCI into multiple stages shortens the duration of procedure in each stage, which has a number of benefits such as lower risk of contrast-induced nephropathy and less radiation exposure. Although multistage PCI may potentially be safer and more effective than one-staged PCI, such benefits have not yet been established.[208] Therefore, one-staged PCI should be the standard approach even in patients with multivessel disease. In practice, however, multistage PCI is often chosen over one-staged PCI for different reasons, which vary and are related to renal impairment, contrast dose, disease complexity, ACS, radiation dose, patient age, impaired cardiac function, and procedural complications, among others.[209]

The SCAI of the USA published a consensus statement on staged PCI in 2012.[210] It specifies that one-staged PCI should generally be performed when: (1) the patient has severe functional stenosis (=high degree of ischemia) and requires PCI in non-main lesions, considering symptoms and prognosis; (2) the patient has no comorbidities, has undergone successful intervention of the main lesion, and can tolerate additional contrast dose and radiation exposure; and (3) the patient has requested PCI and delaying the procedure is expected to result in loss of benefits.

Due to the inherent limitations of PCI in terms of safety (e.g., the use of contrast dye, radiation), the treating physician is required to identify the lesion(s) in which PCI or ischemia evaluation is planned, plan the procedural sequence, select a technique, decide whether to perform the procedure in a one-staged or multistage manner, and communicate all the information to the patient in advance. When unforeseeable events occur, the planned procedure should be modified as needed in an appropriate manner.

V. Revascularization in Special Populations

1. HF, Impaired Left Ventricular Function (Table 16)

CAD is the most frequent cause of chronic HF. Patients with left ventricular dysfunction are at risk of sudden cardiac death with or without revascularization. The indication for implantable cardioverter-defibrillator should always be considered in these patients.[211]

1.1 Evidence in Chronic HF Patients

For ischemic HF patients, coronary artery revascularization is recommended because it can achieve a higher long-term survival rate compared with medical therapy alone.[135,211] Nevertheless, consensus has not been reached on the optimal revascularization technique for these patients.

The STICH study was a RCT comparing CABG with medical therapy.[135] One of the analyses performed in the study revealed that patients with impaired left ventricular function (LVEF <35%) had an acceptable 30-day mortality rate of 5.1% after CABG.[135] In the STICH Extension Study (STICHES), the 10-year survival rate of patients who underwent CABG with medical therapy was significantly higher compared with patients who received medical therapy alone, supporting the finding in the STICH study.[212]

In Japan, the observational CREDO-Kyoto PCI/CABG Registry Cohort-2 reported post-CABG prognosis of patients grouped by cardiac function. Among 1,877 patients who underwent isolated CABG, outcomes were compared in patients with normal cardiac function (LVEF >50% and no HF, n=1,489), patients with systolic failure (LVEF ≤50% and with HF, n=236), and patients with diastolic failure (LVEF >50% and with HF, n=152).[213] Although the 30-day mortality rate was significantly higher in the systolic failure group (3.0%) compared with 0.5% in the normal group and 0.7% in the diastolic failure group (P=0.003), the 5-year all-cause mortality rate was highest in the diastolic failure group (32% vs. 14% in the normal group and 27% in the systolic failure group; P<0.001). After adjustment for confounding factors, the 5-year mortality rate of the diastolic failure group was higher than in the normal group and similar to the systolic failure group.

No RCTs have compared PCI with medical therapy in patients with impaired left ventricular function. Only a few observational studies have investigated the outcomes of PCI alone in that patient population. In a retrospective study in 5,377 patients (≥70% underwent PCI with DES), the target lesion revascularization (TLR) rate at 1 year following PCI was not different among 4 LVEF subgroups (>50%, 41–50%, 25–40%, and <25%), but ST occurred more frequently in the <25% and 25–40% groups compared with the >50% group.[214] In a prospective observational study of 839 patients with chronic total occlusion (CTO; successful PCI in 93.6%), the incidence of cardiovascular events over 2 years was similar across the LVEF ≥50%, 35–50%, and ≤35% subgroups. In successful PCI patients with LVEF ≤35%, the mean LVEF increased from 29.1±3.4% to 41.6±7.9%.[215] Advances in PCI technology and medical therapy may affect the clinical outcomes, and patient demographics often vary significantly between patients with and without impaired left ventricular function. Therefore, interpretation of these observational data always requires caution.

No RCT has compared the outcome of PCI and CABG in patients with impaired left ventricular function. There are only reports of subgroup analysis in RCTs or from observational studies. In the subgroup analysis of the EXCEL study that compared PCI with 2nd-generation everolimus-eluting stent (EES) and CABG in patients with LMCA disease (SYNTAX score ≤32), the incidence of the primary endpoint (3-year all-cause death, stroke, and myocardial infarction) revealed no significant difference between the PCI (20.4%) and CABG (18.2%) groups among patients with <50% LVEF (111 patients in the PCI and 115 in the CABG group, respectively).[193] The CREDO-Kyoto PCI/CABG Registry Cohort-2 was an observational study of PCI with 1st-generation DES. There were 3,584 patients with 3-vessel or LMCA disease among 15,939 who underwent revascularization for the first time. Of these patients, the propensity score-adjusted 5-year all-cause mortality and cardiac death rates were similar between PCI and CABG among those with preserved left ventricular systolic function (LVEF >50%, 2,676 patients). In patients with impaired systolic function (LVEF ≤50%, 908 patients), the PCI group had higher all-cause death (HR, 1.49; 95% confidence interval [CI], 1.04–2.14; P=0.03) and cardiac

Table 16. Recommendation and Evidence for Revascularization in Patients With Chronic Heart Failure or Left Ventricular Systolic Dysfunction (LVEF ≤35%)

	COR	LOE
Revascularization in patients with myocardial viability*	I	B
CABG in patients with a significant stenosis in LMCA or with a lesion of equivalent clinical significance (e.g., severe stenoses in proximal LAD and proximal LCX)	I	C
CABG in patients with a significant stenosis in LAD or multivessel disease intended to reduce death or hospitalization due to cardiovascular disease	I	B
PCI in patients with coronary artery anatomy amenable to PCI	IIa	C
SVR for left ventricular aneurysm or ventricular arrhythmia unresponsive to medical therapy	I	C
CABG+SVR with anterior wall incision in patients with impaired left ventricular function and anterior wall scar who are expected to achieve, if SVR is performed simultaneously, a postoperative left ventricular endsystolic volume index of 40–80 mL/m²	IIa	B
CABG+SVR with posterior wall incision in patients with impaired left ventricular function and posterior wall scar	IIb	C
SVR in patients in whom SVR is considered high risk	III	B

*See Chapter 1.4, page 484. CABG, coronary artery bypass grafting; COR, class of recommendation; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMCA, left main coronary artery; LOE, level of evidence; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SVR, surgical ventricular reconstruction.

death (HR, 2.39; 95% CI, 1.43–3.98; P<0.01) rates compared with the CABG group.[216] Among observational studies of PCI using newer-generation DES, the New York State registry reported a comparison of PCI with 2nd-generation EES and CABG in multivessel disease patients with impaired left ventricular systolic function (LVEF ≤35%).[217] Over the median 2.9-year follow-up of 2,126 propensity score-matched patients (1,063 each underwent PCI and CABG), the all-cause mortality rate of the patients with PCI (HR, 1.01; 95% CI, 0.81–1.28; P=0.91) was similar to that of the patients with CABG. PCI was associated with an increased risk of late myocardial infarction, especially among patients who had incomplete revascularization or underwent repeat revascularization. CABG on the other hand was associated with an increased risk of stroke. The report concluded that PCI may be a meaningful option in multivessel disease patients with impaired left ventricular function if complete revascularization is feasible.

Generally, CABG achieves a higher long-term survival rate and decreases long-term cardiovascular events more than PCI in patients with moderately or severely impaired left ventricular function (LVEF <50%).[213,218] Nevertheless, the choice of CABG or PCI should be made by the Heart Team with careful assessment of the patient's clinical presentation, anatomy of CAD, the expected degree of revascularization (or if complete revascularization is feasible), myocardial viability, the presence or absence of valvular heart disease, and other comorbidities.

1.2 PCI

A registry of PCI with newer-generation DES has reported no difference in survival benefit between PCI and CABG.[217] However, this is not sufficient to prove the efficacy of PCI in patients with impaired left ventricular function, because of the absence of RCTs comparing PCI against medical therapy or CABG. In a patient with impaired left ventricular function, PCI should be considered only if the patient has myocardial viability, demographic or other characteristics that make CABG inappropriate, and lesions for which PCI is anatomically indicated (**Table 16**).

Observational studies have shown that prophylactic intra-aortic balloon pumping (IABP) during PCI in high-risk patients decreases mortality and major complications compared with rescue IABP.[219,220] In the BCIS-1 study, an RCT of patients with extensive CAD and impaired cardiac function (mean LVEF, 23.6%), no differences were observed in the outcomes of PCI between the group with and without prophylactic IABP. However, IABP was required during PCI by 12% of the group without the prophylactic procedure.[221] Routine prophylactic IABP is not recommended during PCI in patients with impaired left ventricular function. Nevertheless, necessary preparation should be made for timely IABP during PCI in high-risk patients.

The recently launched Impella® is a catheter-mounted small device for circulatory assistance. It provides greater hemodynamic support than IABP and can decrease the left ventricular afterload that is increased by veno-arterial extracorporeal membrane oxygenation. In Japan, Impella is indicated for patients with acute left HF complicated by cardiogenic shock and not responding to medical therapy. A multicenter retrospective study that investigated the outcomes of PCI performed on unprotected LMCA disease in 36 patients with ACS complicated by cardiogenic shock reported that the 30-day survival rate was significantly higher in patients who had Impella 2.5 placed prior to PCI compared with those who had the device placed after PCI (48.1% vs. 12.5%, P=0.004).[222] In an RCT comparing Impella and IABP in 48 patients with AMI complicated by cardiogenic shock, no statistically significant differences were observed in the 30-day or 6-month mortality rate.[223] Evidence to support the use of Impella in elective PCI in patients with impaired left ventricular function is insufficient to date. We await accumulation of data through RCTs and in registries.

1.3 CABG

CABG is commonly performed "off-pump" (OPCAB). In patients with impaired cardiac function, however, on-pump coronary artery bypass (ONCAB) is also frequently selected because of the risk of hemodynamic perturbations during heart displacement. In a clinical trial that compared OPCAB and ONCAB, 934 patients with impaired cardiac function (LVEF ≤30%) who underwent OPCAB or ONCAB under cardiac arrest were followed for an extended period and matched by baseline characteristics for comparison of outcomes. The incidence of perioperative myocardial infarction was higher for ONCAB (3.8% vs. 1.3%, P=0.04), but no statistically significant differences were noted in perioperative mortality rate or the incidence of other complications, including stroke.[224] In the long term, the repeat revascularization rate was higher for the OPCAB group, but without a statistically significant difference in mortality rate.

In patients with impaired cardiac function, ONCAB is occasionally performed on a beating heart for myocardial preservation. In a study that allocated patients with impaired cardiac function (LVEF ≤35%) to beating-heart ONCAB or OPCAB and compared early postoperative outcome, the number of bypass grafts was significantly larger in the beating-heart ONCAB group (3.7±0.8 vs. 2.8±0.6, P<0.001), together with significantly higher postoperative LVEF (baseline LVEF was similar between the groups).[225] No significant differences were observed in perioperative mortality or complications. Multivariate analysis in the study indicated neither beating-heart ONCAB nor OPCAB as a predictor of perioperative death or complications. Another study compared the outcomes of beating-heart ONCAB, OPCAB, and traditional CABG in patients with 37% mean LVEF and a EuroSCORE of 12, and reported that beating-heart ONCAB decreased perioperative cardiac complications and was safe and effective.[226] Because these clinical trials only had small patient populations without collection of long-term outcome data, however, they only have limited clinical relevance.

1.4 Surgical Ventricular Reconstruction (SVR)

1.4.1 Goals

The goals of SVR for the treatment of ischemic heart disease are summarized as volume reduction of the left ventricle, myocardial scar exclusion, and left ventricular reshaping.

Dilatation of the left ventricle by post-infarction remodeling is associated with a lower survival rate,[227] whereas successful left ventricular volume reduction (endsystolic volume index [ESVI] <60 mL/m^2) after SVR is associated with a higher survival rate.[228–230] Moreover, further left ventricular remodeling can be induced by increased neuro-

hormonal activity in patients with a dilated left ventricle,[231] but SVR can decrease this activity.[232] On the other hand, because left ventricular volume reduction by SVR may decrease stroke volume,[233] excess volume reduction should be avoided.

An increase in the left ventricular akinetic area due to myocardial ischemia decreases stroke volume, though subsequent left ventricular dilatation compensates for the decrease.[234,235] Exclusion of the scar in SVR can decrease the left ventricular volume without reducing the stroke volume.[236]

The relationship between myocardial fiber contraction and LVEF is affected by myocardial fiber orientation, which is also associated with left ventricular shape. Left ventricular ejection gets more inefficient as the left ventricle becomes more spherical in post-infarction remodeling.[237] In contrast, SVR focusing on restoration of a conical left ventricular shape was associated with a higher survival rate than that focusing on reducing left ventricular volume without restoring the shape.[238]

1.4.2 Benefits

The STICH trial, an RCT that investigated the benefits of SVR on the ischemic heart with left ventricular dysfunction (baseline LVEF <35%), compared 499 patients who underwent isolated CABG and 501 patients who underwent CABG+SVR, and concluded that adding SVR to CABG did not improve survival.[239] However, there has been criticism of the study design.[240] A Japanese retrospective, multicenter study (SURVIVE) reviewed 293 CABG patients with baseline LVEF <40% and indicated that SVR with anterior left ventricular wall incision achieved a significant decrease in ESVI and an increase in LVEF. The study also reported that postoperative LVEF affected patient survival and concluded that SVR could improve survival by increasing LVEF.[241]

1.4.3 Indications

The indication of SVR should be determined comprehensively by considering several factors, including the extent of left ventricular remodeling, surgical risk, and left ventricular shape.

The patients for whom SVR can improve survival (i.e., responder to SVR) are considered to be those with moderate left ventricular remodeling, not those with severe (too late) or mild (too early) remodeling.[242] However, previous studies failed to demarcate the lower and upper limits of the extent of left ventricular remodeling for the indication of SVR in terms of baseline left ventricular ESVI. Instead, the significance of postoperative left ventricular volume in the identification of a responder to SVR was suggested in the STICH trial, where CABG+SVR was associated with a higher survival rate than isolated CABG in those with postoperative ESVI $\leq 70\,mL/m^2$.[230] The SURVIVE study also reported that the postoperative ESVI could demarcate the responder to SVR: an increase of LVEF by SVR had a survival benefit only in patients with postoperative ESVI of 40–80 mL/m^2. The SURVIVE study concluded that estimation of postoperative ESVI could help identify responders to SVR, also showing an equation to estimate postoperative ESVI using the extent of baseline left ventricular remodeling and surgical technique.[241] Thus, those who are estimated to have postoperative ESVI of 40–80 mL/m^2 can be considered responders to SVR.

On the other hand, improvement of survival by adding SVR to CABG does not always substantially contribute to long-term survival. For this reason, estimation of survival time after SVR should be performed for individual candidates using risk prediction models after SVR.[243,244] The Japanese retrospective study (J-STICH) reviewed 596 patients who underwent SVR and identified the baseline INTERMACS level, severity of mitral regurgitation (MR), LVEF, and age as the independent predictors of postoperative mortality. The postoperative 3-year survival rates of the low-, intermediate-, and high-risk groups categorized by risk scores assigned using the predictors were, respectively, 93%, 81%, and 44%.[243] Therefore, SVR should be beneficial for responders if they are categorized as low or intermediate risk. In high-risk patients, however, achieving favorable long-term survival is probably difficult even for responders to SVR. Palliative care, ventricular assist device implantation, or heart transplant are more practical options in such patients.[241]

SVR was originally developed for the treatment of left ventricular aneurysm, and subsequently adopted for ischemic cardiomyopathy with a large akinetic area. Although a significant difference was reported in post-SVR survival time between left ventricular aneurysm and ischemic cardiomyopathy,[245] other reports indicate that left ventricular shape is irrelevant to the outcomes of SVR.[246,247] Despite the absence of consensus, baseline left ventricular shape does not appear to determine the indication of SVR. On the other hand, SVR should be considered when myocardial scar, such as in a left ventricular aneurysm, is associated with formation of a giant left ventricular thrombus or ventricular arrhythmia that are refractory to medical treatment.

The extent of residual myocardial viability has been considered to be associated with survival after coronary revascularization,[248] and also helps predict the outcome of SVR. In contrast, a subanalysis of the STICH trial demonstrated that there was no interaction between myocardial viability and the type of the procedure (isolated CABG vs. CABG+SVR) with respect to mortality.[249] There remains no consensus on how myocardial viability should be treated when determining the indication of SVR.

1.4.4 Variations in SVR

Various techniques have been reported for SVR in terms of the use of an intraventricular patch, the location of the left ventricular incision, myocardial resection, and postoperative ventricular shape.[250–253] As there is no study to date that can conclude which is the best procedure for SVR, it is recommended to carefully select the procedure that seems most appropriate for the patient, considering the location of the left ventricular incision according to the scar sites,[254] prevention of excess volume reduction using dedicated sizers,[255] and restoration of left ventricular shape, etc.

2. DM

2.1 DM and CAD

An MHLW report published in 2016 stated that almost 24% of the Japanese population had or were at risk of diabetes (including ~10 million "strongly suspected" to have diabetes and another 10 million at risk).[256] CAD is one of the leading causes of death among DM patients,[257–259] killing almost 3-fold more DM patients than non-DM patients.

Even without a prior history of CAD, the incidence of myocardial infarction in DM patients is about 6-fold higher than in non-DM patients.[260]

Many DM patients have a number of comorbidities, and CAD in DM patients tends to have characteristics that make revascularization difficult, such as diffuse and microvascular disease. CAD in DM patients is also often asymptomatic, which can delay revascularization, making detection of CAD particularly important for DM patients. DM is an important determinant of the revascularization technique to be used and choosing an optimal revascularization technique requires holistic assessment because of the wide variation in clinical presentation among DM patients.

Over 40% of Japanese patients who undergo revascularization in the clinical setting have DM,[261] which is significantly high compared with 20–30% in Europe/US.[262]

2.2 PCI (Table 17)

CAD in DM patients is often LMCA disease, multivessel disease, and/or diffuse disease, and DM patients typically have small vessels and/or severe calcification. Also, hyperglycemia has adverse effects on the vascular endothelium. These features seen in DM patients tend to make PCI unsuitable or selection of a suitable PCI device difficult. DM therefore lowers the lesion success rate and impairs the long-term prognosis of CAD. The incidence of in-stent restenosis (ISR) was high during the BMS era but decreased, even among DM patients, after the advent of DES. The SIRIUS study compared DES and BMS in DM patients.[263] A SES was placed in 279 DM patients and achieved a significantly lower TLR rate compared with BMS at 8 months after stent placement. Newer-generation DES have improved the outcome of PCI compared with 1st-generation DES in DM patients, but the extent of this improvement is smaller compared with the improvement achieved in non-DM patients, indicating the difficulty of PCI in DM patients.[264–266]

The superiority of CABG to PCI in DM patients, particularly for DM patients with multivessel disease, has been demonstrated in a number of clinical trials.[144,172] In the BARI study, the cardiac mortality rate over 5.4 years following revascularization of multivessel disease was significantly lower in the CABG group compared with the balloon PCI group (5.8% vs. 20.6%).[267] The difference in mortality rate was maintained 7 and 10 years after revascularization.[131,268,269] In the FREEDOM study, the incidence of major adverse cardiovascular events in the 5-year follow-up period was 26.6% in the PCI group and significantly lower in the CABG group (18.7%). The difference between the groups was due to the greater number of all-cause deaths and myocardial infarctions in the PCI group.[172] In 2018, a pooled analysis of 11 comparative studies in multivessel and LMCA disease patients was published.[173] According to the analysis, the 5-year survival rate for multivessel disease was no different between CABG and PCI among non-DM patients, but was significantly higher for CABG among DM patients. In addition, more favorable survival was achieved after CABG than after PCI in DM patients with left ventricular dysfunction.[270]

Preventing myocardial infarction and death from CAD (secondary prophylaxis), together with the relief of angina pectoris is particularly important for DM patients. Also, DM patients with multivessel disease are likely to receive a survival benefit from CABG. These findings should be remembered when the Heart Team defines the goal of coronary artery revascularization in a DM patient.

Table 17. Recommendation and Evidence for PCI in Diabetic Patients

	COR	LOE
Use of 2nd-generation or later DES in stenting	I	B
Interruption of metformin for 48 h before/after PCI	I	C

COR, class of recommendation; DES, drug eluting stent; LOE, level of evidence; PCI, percutaneous coronary intervention.

Table 18. Recommendation and Evidence for CABG in Diabetic Patients

	COR	LOE
Choose CABG as first-line treatment for multivessel disease	I	A
Aim for post-intervention blood glucose levels of <180 mg/dL	I	B
Carry out artery grafting using skeletonized BITA as the first choice	IIa	A
Skeletonized harvesting of ITA	IIa	A

BITA, bilateral internal thoracic artery; CABG, coronary artery bypass grafting; COR, class of recommendation; ITA, internal thoracic artery; LOE, level of evidence.

2.3 CABG (Table 18)

2.3.1 Impact on Outcome

The outcome of CABG in DM patients is generally poorer than in non-DM patients.[271–273] Herlitz et al reported from a 2-year follow-up of CABG patients that the mortality rate within 30 days and between 30 days and 2 years after CABG were respectively 3% and 3.6% in non-DM patients compared with 6.7% and 7.8% in DM patients.[273] The incidence of postoperative complications is also higher in DM patients. In particular, insulin therapy is a notable risk factor in postoperative death and complications.[271,272,274–280]

2.3.2 Benefits of OPCAB

Greater benefits of OPCAB are generally expected in patients with more severe DM. The use of extracorporeal circulation carries a greater risk in DM patients than in non-DM patients.[281] A few studies have compared OPCAB against ONCAB in DM patients. Some reporting more favorable results for OPCAB[282–284] noted less short-term adverse events (death, infections, cardiac events, cerebral infarction, renal failure) and shorter postoperative hospital stay.[285,286] There are recent reports throwing doubt on the benefits of OPCAB.[287–289] However, many of the reports disputing the benefits of OPCAB only pointed out the way OPCAB had been performed, rather than refuting the potential benefits of OPCAB. Most reports published by people working at experienced institutions recommend OPCAB.

2.3.3 Graft Selection for Diabetic Patients

Most studies reporting the effects of DM on graft patency

have noted that DM has little effect on the long-term patency of arterial grafts.[290–294] One report indicated that saphenous vein grafts (SVGs) have low long-term patency in DM patients.[294]

Bilateral ITA (BITA) grafting has a favorable long-term outcome in both the general patient population[295,296] and DM patients.[297] A number of recent studies have investigated the use of arterial grafts, because of their increased popularity, and have shown that the use of multiple arterial grafts (MAG), primarily BITA, can significantly improve the outcome of CABG in DM patients.[281–286,297–305] However, the risk of mediastinitis with BITA is a concern in DM patients.[306–309] Many reports have noted mediastinitis will not increase when skeletonized BITA is used.[281,298–301] A meta-analysis published by Kajimoto et al in 2015 reported that the incidence of mediastinitis was no different between skeletonized BITA (1.4%) and skeletonized single ITA (SITA; 1.5%).[281] The above reports show that skeletonized BITA is an important option for CABG in DM patients. Nevertheless, its use should be carefully considered per patient as the risk of surgical site infection will increase in the presence of risk factors such as obesity in women and chronic obstructive pulmonary disease.[310]

2.3.4 Postoperative Glucose Control

Many reports agree that postoperative hyperglycemia is associated with postoperative complications and death.[311–316] In particular, hyperglycemia within 2 days after CABG has been reported as an independent risk factor of mediastinitis.[315,316] No optimal postoperative glucose levels have been established for DM patients. However, the STS notes that ≥150 mg/dL is associated with increased complications and mortality rate, and proposes 100–150 mg/dL as the reference range.[317] Some recent reports argue that moderate control (up to 180 mg/dL) rather than rigorous control correlates with less frequent deaths and complications.[318,319] In this guideline, <180 mg/dL for glucose levels after CABG is loosely recommended.

3. CKD

CKD affects 13.3 million Japanese, or approximately 13% of adults, making CKD a new "national disease". Because CKD is more prevalent in aged individuals,[320] it poses a greater problem in apidly aging populations. The prevalence of CAD is high among CKD patients, who areare estimated to be 1.9-fold more likely to develop CAD than non-CKD patients.[321] Even early-stage CKD, let alone end-stage renal disease requiring dialysis, is known as a significant risk factor of cardiovascular death.[322] CKD patients are more likely to die from cardiovascular disease than from end-stage renal disease.[323] Cardiovascular disease comprises about 50% of all deaths of CKD patients. Management of CAD, including revascularization, is therefore of great importance, but there have been few RCTs in CKD patients, limiting evidence to the results of observational studies and subgroup analyses of large-scale RCTs.

3.1 Assessment of Renal Impairment

In 2002, the National Kidney Foundation (K/DOQI) published their definition, diagnostic criteria, and disease stage classification of CKD.[324] Their diagnostic criteria are made up of (1) kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney (pathological abnormalities, abnormalities in the composition of the blood or urine, or abnormalities in imaging tests), with or without decreased GFR, and (2) GFR <60 mL/min/1.73 m^2 for ≥3 months. The K/DOQI defines the diagnosis of CKD as being when the patient fulfills either or both of the criteria.

Estimated GFR (eGFR) is calculated using serum creatinine (SCr), age, and sex. The Japanese Society of Nephrology recommends the following eGFR formula for the treatment of CKD in the clinical setting:[325]

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \quad (+ \text{"}\times 0.739\text{" for female}).$$

3.2 Degree of Renal Impairment and Outcome of Revascularization

CKD is recognized as a significant factor associated with the early and long-term outcomes of revascularization for CAD patients.[326,327] According to an analysis of the STS's National Adult Cardiac Database (480,000 cases of CABG between the years 2000 and 2003), eGFR before CABG was the strongest predictor of perioperative death.[326] Although early outcomes of CABG are poor in CKD patients compared with non-CKD patients, a study reported that CKD patients who are discharged alive after CABG have good long-term survival.[328] Also, although the risks of early postoperative dialysis and death are higher for CABG than for PCI in CKD patients, long-term survival after CABG equals or exceeds that after PCI.[329,330]

There is an analysis of the relationship between renal function and treatment outcome in 4,584 patients who had severe coronary artery stenosis and underwent cardiac catheterization at Duke University Medical Center between 1995 and 2000.[331] According to the analysis, the 5-year survival rate was significantly higher for the PCI group compared with the medical therapy group among patients with normal renal function or mild to moderate renal impairment, but PCI did not improve survival in patients with severe renal impairment. In patients who underwent CABG, 5-year survival was significantly higher compared with the medical therapy group, regardless of renal function. Long-term survival was also significantly more favorable with CABG than PCI in patients with severe renal impairment. CKD is a common comorbidity in CAD patients, and the severity of CKD is a determinant of the outcome of revascularization and an important factor in treatment planning.

Of the 15,939 patients in the CREDO-Kyoto PCI/CABG Registry Cohort-2, 14,706 were discharged alive, had renal function data, and were stratified into 4 groups by baseline eGFR and with/without dialysis for analysis of the incidence of cardiovascular events (myocardial infarction or death) over 3 years.[332,333] Of the 12,588 who underwent PCI, the 3-year event-free survival rate in 7,899 patients with normal renal function and 3,780 patients with mild renal impairment was respectively 91.2% and 85.3%. In 461 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and 448 on dialysis, it was 66.7% and 61.5%, respectively. Of the 2,118 patients who underwent CABG, the 3-year event-free survival rate was 91.9% in 1,070 patients with normal renal function, and 87.1% in 787 patients with mild renal impairment, similar to the PCI group. In 147 patients with severe renal impairment and 124 patients on dialysis, however, it was respectively 75.9%

and 72.8% and significantly higher than in the PCI group. Subgroup analysis of the ARTS study reported that CABG decreases repeat revascularization compared with PCI in multivessel disease in patients with moderate CKD.[334] Strong evidence indicates that CABG can reduce repeat revascularization and offers a greater survival benefit than PCI for complex CAD patients with severe renal impairment.

3.3 Patients on Dialysis

Of all CKD patients, those on dialysis have a particularly poor prognosis. The incidence of cardiovascular death in CKD patients on dialysis is 10–20-fold that in the general population.[335] This increased risk is suspected to be caused by the high prevalence of CAD among these patients.[336] CAD in CKD patients on dialysis warrants special consideration. However, there are few reports, with a limited number of cases, of revascularization in maintenance dialysis patients.

A report comparing the outcomes of CABG and PCI against those of medical therapy in CAD patients on dialysis noted that CABG achieved better long-term survival than medical therapy. PCI also offered better survival than medical therapy.[337] A data analysis by the US Renal Data System compared the long-term outcome of revascularization by CABG or PCI between 1995 and 1998 in American patients on dialysis (6,668 underwent CABG, 4,836 received balloon dilatation alone, and 4,280 underwent stent placement).[338] The 2-year survival rate was 56.4% for CABG, 48.2% for balloon dilatation, and 48.4% for stent placement, revealing the superiority of CABG. The CREDO-Kyoto PCI/CABG Registry Cohort-2 also compared CABG (n=130) and PCI (n=258) among propensity-matched patients on dialysis, and reported a significantly higher incidence of cardiovascular death and sudden death, as well as a significantly higher repeat revascularization rate, for PCI but the long-term all-cause mortality rate was similar between CABG and PCI.[339]

Even today with the widespread use of DES, the benefits of CABG are generally considered to exceed those of PCI. Because maintenance dialysis patients are more likely to undergo surgery than CAD patients in general, treatment for CAD should be chosen by considering the performance status and vital prognosis of each patient.

3.4 PCI (Table 19)

Precautions for contrast-induced nephropathy (CIN), hemorrhagic complications, and vascular access site are needed for PCI in CKD patients. The incidence of CIN is high. CIN has a negative effect on the prognosis of CKD (see **Chapter VIII**, page 537 for more information). CKD is also a risk factor for hemorrhagic complications during dual antiplatelet treatment (DAPT). Precautions are also needed for concomitant drug dosing and adverse reactions. Patients with CKD often have calcified coronary artery lesions, and calcification is particularly severe in CKD patients with DM. Calcification increases the likelihood of incomplete stent dilatation and weak contact between the stent and artery wall in PCI, and both of these are risk factors for procedural complications such as ISR and ST. In cases where preservation of blood access for dialysis should be considered, an approach site other than the radial artery (RA) must be selected. In such cases, the risk of bleeding complications increases.

A study comparing the outcome of PCI with BMS (n=204) and DES (n=301) reported a significantly lower TLR for DES in a 6-year period.[340] Even with DES, however, the restenosis rate was higher in patients on dialysis compared with non-dialysis patients.[341] Patients on dialysis tend to have complex disease such as severe calcification and elongated lesions that make stent insertion difficult or require use of the Rotablator®. Skilled hands are also required to perform PCI in dialysis patients.

The prevalence of CAD is higher in dialysis patients than in non-dialysis patients. Often CKD patients have asymptomatic coronary artery stenosis even before starting dialysis. Because CAD can lead to serious cardiac events or death, rigorous screening is recommended for early detection and treatment of CAD in dialysis patients.

3.5 CABG (Table 20)

3.5.1 Procedure Selection

OPCAB has been associated with better operative outcomes than ONCAB in patients with renal impairment.[342–344] A number of observational studies in CKD patients report superiority of OPCAB, with statistically significant differences in the length of postoperative ICU stay, intubation time or transfusion volume, but few have reported significant benefits in surgical or long-term mortality. There is skepticism about the benefits of OPCAB in patients with moderate CKD. There are reports indicating that OPCAB does not lessen the worsening of renal impairment or the risk of renal replacement therapy,[345,346] and does not affect dialysis in the long term.[347]

3.5.2 Graft Selection

Bypass graft patency is critical for the long-term outcome

Table 19. Recommendation and Evidence for PCI in CKD Patients

	COR	LOE
Prior risk evaluation of contrast-induced nephropathy based on baseline GFR	I	C
Carry out PCI with contrast dose adjustment considering the risk of contrast-induced nephropathy	I	C

CKD, chronic kidney disease; COR, class of recommendation; GFR, glomerular filtration rate; LOE, level of evidence; PCI, percutaneous coronary intervention.

Table 20. Recommendation and Evidence for CABG in CKD Patients

	COR	LOE
Choose CABG over PCI in multivessel disease to place emphasis on long-term survival	IIa	B
Perform OPCAB for lower perioperative risk	IIb	B

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COR, class of recommendation; LOE, level of evidence; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention.

after CABG. ITA is most often used because of its superior long-term patency. The use of BITA has improved the survival of CKD patients or patients on dialysis.[348,349] However, endothelial function inside the ITA may be affected in CKD patients.[350] BITA is occasionally avoided in dialysis patients because of concerns about deep sternal wound infection (DSWI). However, the frequency of late wound recovery or DSWI is similar with or without BITA use in CKD patients, according to some reports.[348,351] The gastroepiploic artery (GEA) is often avoided as a graft because many CKD patients have sclerotic changes in the splanchnic arteries or require peritoneal dialysis. In addition, the RA, which typically provides vascular access for hemodialysis, cannot normally be used as a graft in CKD patients. Because the SVG deteriorates rapidly in dialysis patients, an arterial graft is generally preferred. Because of the above limitations, however, graft selection should take into account individual conditions in CKD patients.

4. Valve Disease

4.1 Treatment Approach

A slightly different treatment approach is needed for CAD in patients for whom surgical treatment of valvular disease is indicated, and for patients who have valvular disease but first require revascularization for CAD. For revascularization in patients for whom surgery for valvular disease is indicated, CABG is typically performed simultaneously with valvular disease surgery when the risk is acceptable. However, there is very little supportive evidence for such concomitant surgery.[352] For patients who need revascularization for CAD but do not have a surgical indication for valvular disease, coronary artery revascularization should be given priority.

4.2 PCI

4.2.1 Aortic Stenosis (AS; Table 21)

AS is, unless rheumatic or inflammatory in origin, age-related arteriosclerosis/degeneration of the aortic valve and often complicated by CAD.[353] TAVI is mostly performed in aged individuals. According to the large TAVI registry of the STS/ACC TVT, only 37% of patients were free of CAD.[354] A Japanese TAVI registry also reported that about 50% of patients have CAD.[355] Aortic valve replacement (AVR), whether by standard surgery or the less invasive TAVI, carries a high risk of death in patients with both severe AS and CAD.[356–358] Therefore, just as with cardiovascular surgery, coronary angiography for preoperative evaluation is recommended for most patients (excluding young adults) who are scheduled to undergo aortic valve surgery (including TAVI).

Consensus has not been reached on whether PCI should be performed in patients scheduled to undergo TAVI.[358–360] Historically, multicenter studies have reported that PCI prior to TAVI is beneficial. In a meta-analysis published in 2017, however, PCI before TAVI revealed no clear benefits and instead was associated with increased 30-day mortality and vascular complications.[361] Some studies have noted that a residual SYNTAX score and CAD severity are unrelated to outcome after TAVI in asymptomatic patients.[362,363] Available evidence suggests that revascularization prior to TAVI should not be a routine procedure. The decision to perform PCI should be based on the patient's ischemic symptoms.

Table 21. Recommendation and Evidence for PCI Before Aortic Stenosis Intervention

	COR	LOE
Prior review of CAD by Heart Team	I	C
Coronary angiography for preoperative examination (excluding young adults and premenopausal women)	I	C
PCI in severe coronary artery stenosis in patients for whom TAVI is indicated	IIb	A

CAD, coronary artery disease; COR, class of recommendation; LOE, level of evidence; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation.

Ischemia evaluation in severe AS is known to be difficult. Due to left ventricular subendocardial ischemia, fibrosis, and/or hypertrophy, which are often caused by AS, the effect of coronary artery stenosis on ischemia often cannot be determined. Evaluation of the functional severity of stenosis using FFR or other methods is also difficult. Nevertheless, one report noted FFR is capable of reducing unnecessary aortic valve surgeries or revascularization scheduled simultaneously with aortic valve surgery.[364] At the very least, measurement of FFR can be safely performed in severe AS patients.[365]

4.2.2 MR (Table 22)

Just as with AS, CAD complicated by MR is commonly treated by CABG if the MR is operable. In MR patients, ischemic MR is the primary cause of CAD. Because relieving ischemia can sometimes improve the MR, revascularization prior to intervention for the MR may have a beneficial effect on MR to some extent.[366] A study investigating the feasibility of minimally invasive mitral valve surgery after PCI in a small number of patients at a single center reported favorable results.[367,368]

In Japan, a minimally-invasive percutaneous treatment for MR patients who are likely to undergo surgery (e.g., aged individuals) was added to the approved treatments of the National Health Insurance program in 2018. Clinical application of the treatment started immediately. This new treatment is most likely to be applied to functional MR induced by CAD. Revascularization before transcatheter mitral valve repair has case reports[369] only and therefore lacks reliable evidence. A study reported the utility of SYNTAX score II for severity assessment of CAD before

Table 22. Recommendation and Evidence for PCI Before Surgery for MR

	COR	LOE
Heart Team review of CAD prior to percutaneous mitral valve clipping	I	C
Coronary angiography for preoperative examination (excluding young adults and premenopausal women)	I	C
PCI in severe coronary artery stenosis in patients with inoperable ischemic MR	IIb	C

CAD, coronary artery disease; COR, class of recommendation; LOE, level of evidence; MR, mitral regurgitation; PCI, percutaneous coronary intervention.

Table 23. Recommendation and Evidence for Treatment of AS in Patients Undergoing Elective Coronary Artery Bypass Grafting

	COR	LOE
Aortic valve replacement in severe AS	I	C
Aortic valve replacement in moderate AS	IIa	C

AS, aortic stenosis; COR, class of recommendation; LOE, level of evidence.

Table 24. Recommendation and Evidence for Treatment of MR in Patients Undergoing Elective CABG

	COR	LOE
CABG + mitral valve surgery in severe secondary MR	IIa	B
CABG + mitral valve surgery in moderate secondary MR	IIb	C

CABG, coronary artery bypass grafting; COR, class of recommendation; LOE, level of evidence; MR, mitral regurgitation.

percutaneous mitral valve clipping.[370] The SYNTAX score II may be referenced by the Heart Team, though it does not provide generalizable data for this guideline. The combination of revascularization and valvular disease therapy should be assessed on a per-patient basis.

4.3 CABG

4.3.1 AS (Table 23)

In Japan, the number of valvular disease surgeries is on the rise while the number of patients undergoing CABG is in decline. In 2015, 8,561 patients underwent AVR. Of these, 28.8% (2,492 patients) underwent simultaneous CABG,[371] a significant rise from 16% in 2005.[372] The increase is probably due to the increased age of patients and the increased severity of arteriosclerosis. The reported mortality rate for CABG+AVR varies from 1.3% to 14.1%,[373] but is apparently higher than the mortality rate for isolated CABG (mortality for AVR alone was 2.0% in 2015 in Japan).[374,375]

Since the reports of high mortality rates (14–24%) for delayed AVR performed on nonsignificant AS remaining after the initial CABG,[376,377] AVR has come to be recommended even for moderate AS. The ECC/EACTS deleted the recommendation of AVR for moderate AS in their recent guidelines published in 2017. The recent development, popularity, and reported favorable and consistent outcomes of TAVI are enabling new treatment strategies, such as putting patients with moderate AS on follow-up until TAVI becomes necessary.[378]

4.3.2 MR (Table 24)

Guidelines on MR should be referenced for the applicability of mitral valve surgery simultaneously with CABG in patients with severe MR.[379–385] Ischemic MR is the primary concern when simultaneous surgery for CAD and MR is considered. Ischemic MR is (1) a mitral valve disease that occurs secondary to and as a result of CAD (2) in the absence of rheumatic heart disease, (3) mitral valve disease, and (4) congenital heart disease. In other words, ischemic MR is functional mitral valve disease resulting from the pulling of the tendinous cords by repositioning of the posterolateral papillary muscle.[386,387] In theory, relief of ischemia can also alleviate or resolve functional (or ischemic) MR. When left ventricular remodeling is not reversible, however, mitral valve intervention becomes necessary.

On the clinical course of MR after CABG, there is a report of occasional worsening even in patients with only moderate MR (on transesophageal echocardiography during CABG).[388] The possibility of transesophageal echocardiography under anesthesia underestimating the severity of MR was also reported.[389] Therefore, whether MR in patients with ischemic MR requiring subvalvular intervention can be successfully treated by CABG currently cannot be predicted reliably. Cautious evaluation in advance is advised.

For moderate MR, there are reports of aggressive surgery achieving favorable outcomes,[390,391] while others have indicated CABG with or without mitral valve surgery achieves similar survival rates.[392,393] CABG alone in moderate MR patients has relieved MR immediately for only a short period, followed by worsening in many patients.[394–396] There is a report arguing that MR by itself is a risk factor of postoperative survival.[397] Isolated CABG relieved MR in another report.[398] The CTSN study conducted in the face of these mixed results produced no conclusive evidence, only reporting similar survival rates and cardiac event-free rates as well as similar left ventricular remodeling between CABG with and without mitral valve surgery.[399,400] In Japan, OPCAB is often performed in isolated CABG. There is no doubt that clinicians now prefer to avoid mitral valve intervention.

5. PAD

5.1 Carotid Artery Disease

5.1.1 Prevalence of Complications and Mechanism of Onset of Cerebral Infarction

Cerebral infarction is a serious perioperative complication in patients who undergo PCI or CABG for the treatment of CAD. The incidence of perioperative cerebral infarction is about 0.3–0.4% after PCI,[172,401] and 1.1% after CABG according to the nationwide survey conducted by the Japanese Association for Coronary Artery Surgery.[402] There is a long, ongoing discussion about prevention of perioperative cerebral infarction after CABG. AF, atherosclerosis of the ascending aorta and arch, left ventricular impairment, and carotid artery disease have been recognized as risk factors for perioperative cerebral infarction after CABG.[403] Screening for carotid artery disease before CABG found severe (≥70%) stenosis in about 5% of patients.[404]

Carotid artery disease can lead to cerebral infarction through decreased cerebral blood flow resulting directly from stenosis or by embolism caused by unstable plaque rupture, but the latter is believed to be the more frequent cause.[405–407] The degree of carotid artery stenosis does not necessarily correlate with the probability of having histologically unstable plaque.[408,409] Screening for intraplaque hemorrhage or ruptured cap by carotid ultrasonography or MRI has been shown to be useful for evaluating the probability of having an unstable plaque.[410] Currently, however, plaque is commonly regarded as stable when

carotid artery disease is asymptomatic, and as unstable otherwise. Carotid artery disease is considered asymptomatic if the patient has no history of or not had symptomatic stroke or transient ischemic attack (TIA) in the past 6 months. It is symptomatic when the patient had a symptomatic stroke or TIA in the past 6 months.[411,412]

5.1.2 Treatment of Carotid Artery Disease (Table 25)

Because the incidence of perioperative cerebral infarction after PCI is low, the common question is whether and what intervention should be done for carotid artery disease in patients undergoing CABG. To determine a suitable treatment, the risk of perioperative cerebral infarction occurring as a result of carotid artery disease and the extent to which the risk can be reduced by treatment must be assessed. For this purpose, brain perfusion scintigraphy is conducted when severe stenosis is suspected in the bilateral carotid arteries.[407] Carotid ultrasonography and MRI also will be useful for determining plaque instability of the carotid artery disease.[409] Neurosurgical proficiency also affects the results of carotid endarterectomy (CEA) or carotid artery stenting (CAS) and constitutes an important factor in treatment decision-making. The risk of perioperative stroke and death preferably should be <3% in asymptomatic patients and <6% in symptomatic patients.[139,413]

There is not a randomized trial about management strategies in patients with concomitant CAD and carotid artery disease. Therefore, whether a treatment is feasible and safe, as well as when to give treatment, should be decided by a multidisciplinary team including a cardiac surgeon, cardiologist, neurosurgeon, and neurologist.[139,411–415] When CABG is performed following CAS, DAPT is advised for 4 weeks in advance.[416,417] The "Japanese Guidelines for the management of stroke 2015" should be referenced for more information about candidate medical therapies and CEA/CAS for carotid artery disease.[418]

Table 25. Recommendation and Evidence for Treatment of Carotid Artery Disease in Patients Undergoing Elective Coronary Artery Bypass Grafting

	COR	LOE
CEA or CAS in severe symptomatic carotid artery stenosis	I	C
Treatment of asymptomatic severe bilateral stenosis or asymptomatic severe unilateral stenosis with contralateral occlusion	IIb	C
Treatment of asymptomatic severe unilateral carotid artery stenosis	III	B

CAS, carotid artery stenting; CEA, carotid endarterectomy; COR, class of recommendation; LOE, level of evidence.

5.2 Other PADs

Regardless of leg symptoms, patients with PAD in a lower extremity have a high prevalence of cardiovascular disease and a high mortality rate.[419] PAD in patients with a history of myocardial infarction, PCI, or CABG is a risk factor of major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, and cerebral infarction).[420,421] The ankle–brachial index (ABI) test is recommended to screen for PAD when coronary angiography is planned for suspected CAD.[412,422] For PCI in patients with PAD, prolonged (24 weeks) DAPT significantly decreased the composite cardiovascular event (death, myocardial infarction, and cerebrovascular event) without increasing hemorrhagic complications compared with short-term (6 weeks) DAPT.[423] Access via the RA is recommended for coronary angiography or PCI in patients with PAD in the lower extremities.[422]

6. Repeat Revascularization

6.1 Restenosis After PCI

6.1.1 Clinical Implication of Follow-up Coronary Angiography

Follow-up coronary angiography after PCI enables comparison of the outcomes of different treatments, as well as the detection of restenosis. Asymptomatic restenosis discovered on angiography 6–8 months after PCI was associated with death by postoperative mortality at 4 years in an observational study.[424] Therefore, the ReACT study investigated the utility of routine follow-up coronary angiography post-PCI. The study assigned 700 post-PCI patients to follow-up with or without coronary angiography and compared the incidence of a composite endpoint (all-cause death, myocardial infarction, emergency hospitalization for ACS, stroke, and hospitalization for HF). The incidence of the composite endpoint over 5 years was no different between the groups, indicating routine follow-up coronary angiography only increases early repeat revascularization.[425] Post-hoc analyses of other RCT data also suggest that routine follow-up coronary angiography in patients with no documented ischemia has no clear clinical relevance while increasing the need for revascularization in the long term (because of the oculo-stenotic reflex).[426,427]

On the basis of these reports, the ESC/EACTS guidelines in 2018 classified the recommendation for follow-up coronary angiography as Class IIb.[64] Routine follow-up coronary angiography is not recommended in this guideline. Follow-up coronary angiography should be restricted to symptomatic patients or patients with signs of ischemia. Follow-up coronary angiography may have some clinical relevance in patients in whom restenosis may immediately result in a fatal event (e.g., LMCA disease). However, because of limited evidence supporting utility in high-risk cases, in general, less invasive techniques should always be considered first.

6.1.2 Restenosis of DES

Stent restenosis is the so-called "Achilles' heel" of PCI, but its incidence has been decreased to approximately 5% since the development of DES. For lesions in which DES placement is difficult (e.g., ISR, small vessel lesion, or side branch lesion of bifurcation disease), the drug-coated balloon (DCB) has been shown to be effective for preventing restenosis. Although the frequency of restenosis after PCI has been decreasing thanks to DES and DCB, the probability of recurrent restenosis after a second restenosis has not decreased much. For this reason, treatment of restenosis is still clinically relevant.

Restenosis of BMS often occurs after 6–8 months, but the degree of stenosis, if it develops, reportedly tends to decrease after this period. On the other hand, DES are associated with late restenosis.[428] The risk of restenosis of the DES varies according to the lesion location and nature of the disease. For example, even new-generation DES fail to effectively prevent restenosis in a highly calcified lesion,

Table 26. Recommendation and Evidence for Repeat Percutaneous Coronary Intervention for Restenosis		
	COR	LOE
New DES placement for in-stent (BMS or DES) restenosis	I	A
Dilatation of in-stent (BMS or DES) restenosis using DCB	I	A
IVUS or OCT/OFDI for evaluation of the mechanism of in-stent restenosis	IIa	C

BMS, bare metal stent; COR, class of recommendation; DCB, drug coated balloon; DES, drug eluting stent; IVUS, intravascular ultrasound; LOE, level of evidence; OCT/OFDI, optical coherence tomography/optical frequency domain imaging.

ostial lesion of the RCA, bifurcation lesion with two-stents, and in dialysis patients.

6.1.3 Mechanism of ISR

Vessel recoil and neointimal thickening are the common mechanisms of ISR. The former is controlled by BMS while the latter is more frequent with BMS than with balloon dilatation. DES has enabled better control of both mechanisms. Mechanical and procedural factors, as well as neointimal proliferation, are known causes of restenosis with DES.

Early DES were prone to restenosis following stent fracture (caused by physical stress) or stent recoil.[429,430] Such types of restenosis have been reduced by the development of thinner DES with improved flexibility.[431] Examples of procedure-related restenosis include incomplete stent expansion and residual stenosis at the stent edge.

6.1.4 Repeat Revascularization by PCI (Table 26)

The utility of DCB for the treatment of ISR is well recognized.[432] DCB is more effective than plain balloon for the treatment of in-stent (BMS or DES) restenosis, with greater benefits against restenosis of BMS than DES.[433] Although late secondary restenosis has been reported after DCB treatment of DES restenosis,[434] recent studies indicate the outcomes of DCB and new-generation DES in the treatment of ISR are similar regardless of the stent type.[435,436] For DCB, better angiographic outcomes were reported when predilatation was performed using a scoring balloon.[437] Careful dilatation of the entire affected segment is needed to decrease the risk of restenosis.[438] This is an important note for DCB dilatation. The etiology of DES restenosis should be analyzed before treatment. IVUS and OCT/OFDI can enable evaluation of the extent of stent expansion and/or the extent/development of neointimal formation. These technologies can also detect stent rupture or recoiling. OCT/OFDI images of the restenosis lesion also provide useful information about tissue characteristics. An association between observations on OCT images and recurrence of restenosis has been noted.[439]

6.2 ST

6.2.1 Background and Types of ST

Subacute ST, which occurs within 2 weeks after stent placement, has been practically eliminated by the use of high-pressure stent implantation and DAPT (aspirin+ thienopyridine). Subsequently, however, very late ST (VLST), which is defined as thrombosis occurring ≥1 year after stent implantation, came to prominence after the introduction of 1st-generation DES. Longer-term DAPT was first applied clinically. However, because of the lower frequency of VLST with the new-generation DES than with 1st-generation DES,[440] short-term DAPT is becoming more of the standard.

It has been difficult to compare different studies of ST because of the varying definitions in use, and also due to the low incidence of ST. Subsequently, the Academic Research Consortium of clinicians/researchers, government, and stent manufacturers developed a new classification system based on the time of onset and level of certainty (**Table 27**).[441]

6.2.2 Causes of ST and Frequency of VLST

The cause of ST varies by the time of onset. Early ST (EST) is caused primarily by incomplete stent expansion or

Table 27. Classification of Stent Thrombosis
By time of onset
1. EST: ≤1 month after implantation
2. LST: 1 month to 1 year after implantation
3. VLST: ≥1 year after implantation
By how diagnosis is confirmed
1. Definite stent thrombosis
[1] Confirmed by angiography
Presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and either acute onset of myocardial ischemic symptoms or signs (electrocardiographic or myocardial enzyme changes) within a 48-h window
[2] Confirmed by pathology
Stent thrombosis confirmed by autopsy or via examination of tissue retrieved following thrombectomy
2. Probable stent thrombosis
[1] Unexplained death within 30 days
[2] Acute MI involving the target vessel territory without angiographic confirmation
3. Possible stent thrombosis
[1] Unexplained death after 30 days

EST, early stent thrombosis; LST, late stent thrombosis; MI, myocardial infarction; VLST, very late stent thrombosis. (From Cutlip DE, et al. 2007.[441])

inefficacy of antiplatelet therapy. Late ST (LST) or VLST may occur as a result of (1) delayed re-endothelialization and prolonged exposure of the strut caused by the eluting drug;[442,443] (2) vascular reactions to stent components, such as localized chronic inflammation and hypersensitivity reaction;[444] (3) late stent malapposition;[445] (4) progression of neoatherosclerosis independent of neointimal formation;[446] or (5) disturbance of blood flow of a physical origin, such as stent failure/recoil.[430,447] Signs of vascular reactions related to hypersensitivity reaction include peri-stent contrast staining (PSS),[448] multiple interstrut hollows,[449] and evagination.[450] IVUS, OCT, or OFDI is useful for evaluation of these phenomena.[451]

With a 1st-generation DES, the incidence of VLST is thought to remain unchanged for years, but in reality the length of follow-up is limited. With a follow-up period of 10 years, one report noted the incidence of VLST started to decline after about 5 years,[452] but another study presented similar incidence between over 1 and 10 years after stent implantation.[453] With the 2nd-generation DES, the incidence of VLST has significantly decreased from that with 1st-generation DES.

6.2.3 Prophylaxis and Prognosis

Antiplatelets administered after stent placement and the duration of antiplatelet therapy vary depending on the patient's clinical condition and the type of stent. Proper stent implantation and appropriate antiplatelet therapy are crucial for prevention of ST.

Antiplatelet therapy is terminated/interrupted by the doctor's decision, prior to surgery, due to occurrence of complications, or because of patient noncompliance. Cessation of antiplatelet therapy by the occurrence of complications or patient noncompliance is undesirable because it is associated with increased clinical events, including ST.[454] Stent failure and PSS confirmed by angiography are associated with ST. DAPT should be continued if stent fracture or PSS is observed with 1st-generation SES.[455]

The outcome of treatment for ST varies by the time of onset. For EST, the thrombosis frequently recurs, with a high likelihood of repeat revascularization. For VLST, low recurrence and repeat revascularization rates have been reported.[456,457]

6.3 Graft Failure After CABG (Table 28)

According to a survey conducted between 2004 and 2014 by the Japanese Association of Thoracic Surgery (JATS), the percentage of redo CABG among all isolated CABG interventions was 1.3–2.4%, peaking in 2004 (2.4%) and decreasing to 1.6% in 2011 and down further to 1.3% in 2014.[458] OPCAB was chosen in 54–62% of redo CABG cases during this time period, which was similar to the ratio with initial CABG. The 30-day mortality rate was 2.1–4.5% for elective CABG, and 9.1–18.5% for emergency CABG, somewhat higher compared with that after the first surgery.

According to a report based on the STS database, the ratio of redo CABG to all CABG performed between 2000 and 2009 decreased from 6.0% to 3.4%, together with a decrease in the operative mortality rate from 6.1% to 4.6%.[459] The mortality rate for primary CABG during the same period was 2.4–1.9%, revealing a significantly higher mortality for redo CABG despite the observed improvement. The mortality rate of redo CABG patients has historically been and is still higher compared with that for initial CABG patients.[460] Nevertheless, this is partly because patients who undergo redo CABG have more comorbidities. A risk-adjusted comparison between initial and redo CABG has shown that the difference in mortality rate is decreasing over time.[459]

Table 28. Recommendation and Evidence for Treatment of Graft Failure After CABG

	COR	LOE
Redo CABG with ITA graft	I	B
Redo CABG for symptom relief in a patient with a patent bypass ITA graft in LAD who has documented ischemia in LCX/RCA and has anatomy unsuitable for PCI	IIa	B

CABG, coronary artery bypass grafting; COR, class of recommendation; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LOE, level of evidence; PCI, percutaneous coronary intervention; RCA, right coronary artery.

A report indicated that OPCAB helps improve the early outcome of CABG,[461] and another study reported a similar long-term outcome between OPCAB and ONCAB.[462] Although there is no consensus on whether OPCAB is superior to ONCAB or vice versa, the frequency of OPCAB is slightly on the rise in the USA.

A randomized study comparing redo CABG and PCI revealed early death was significantly more frequent with redo CABG but with no statistically significant difference in survival or repeat revascularization rate over a 3-year follow-up.[463] Another study that compared redo CABG, PCI, and medical therapy in patients who had a patent left ITA (LITA) and stenosis in the LCX or RCA reported no difference in 1-year survival.[464] In other words, intervention in a non-LITA vessel in patients with a patent LITA does not improve survival and should therefore aim solely for symptom relief.

The use of LITA grafts in LAD disease has favorable early- and long-term outcomes.[465] Recycling of an ITA graft by anastomosing to a different location, such as a BITA graft, has been reported.[466]

7. Patients With AF

7.1 PCI

AF is not a rare comorbidity in patients undergoing elective PCI. The incidence is 5–10% in Europe/USA,[467] and about 8% in Japan according to the CREDO-Kyoto PCI/CABG Registry Cohort-2. The percentage of patients with a score ≥2 on $CHADS_2$ (cerebral infarction risk prediction model with a scale of 0–6; "CHADS" is an acronym for Congestive HF/LV dysfunction, Hypertension, Age ≥75 years, DM, and Stroke/TIA)[468] reached nearly 75%.[469] In the CREDO-Kyoto PCI/CABG Registry Cohort-2, the risks of stroke and all-cause death, and major bleeding among patients with AF were respectively about 2-, 2-, and 1.5-fold higher than in patients without AF over a follow-up period of up to 7 years. In the OACIS study investigating the effects of AF in acute myocardial infarction patients treated with PCI, the prevalence of AF was 12%. AF was not shown to be related to in-hospital death, but was identified as a

Table 29. Recommendation and Evidence for CABG in Patients With AF		
	COR	LOE
Surgical ablation, for sinus rhythm recovery, simultaneous with CABG in patients with AF	IIa	B
Left atrial appendage closure or resection, for cerebral infarction risk reduction, simultaneous with CABG in patients with AF	IIb	C

AF, atrial fibrillation; CABG, coronary artery bypass grafting; COR, class of recommendation; LOE, level of evidence.

significant predictor of death within 1 year.[470] As shown in these studies, both bleeding and mortality risks are high with PCI in patients with AF.

New-onset AF immediately after PCI is rare. According to the EXCEL study, the incidence of new-onset AF within a mean of 3 days after PCI was 0.1%, much lower than that after CABG (18%).[471]

PCI in patients with AF requires anticoagulants to prevent embolism, and antiplatelets to prevent coronary artery events (especially ST). These drugs significantly increase the bleeding risk. In such patients, PCI technique and medical therapy should be chosen in consideration of the bleeding risk (see **Chapter IX**, page 538 for more information). For PCI in these patients, a treatment strategy not requiring long-term DAPT should be selected and performed only after careful comparison with medical therapy and CABG. Percutaneous left atrial appendage (LAA) closure is worth considering for risk reduction when the bleeding risk is very high or when embolism develops during anticoagulation therapy.[472] Percutaneous LAA closure (Watchman device procedure) was used in 2 large-scale RCTs with warfarin (PROTECT AF[473] and PREVAIL[474]) and shown to decrease hemorrhagic stroke, cardiovascular death, and all-cause death significantly over a period of 5 years compared with warfarin, though there was no observed difference in the incidence of stroke.[475]

7.2 CABG (Table 29)

In patients undergoing CABG, the presence of AF is a known poor perioperative and long-term prognostic factor. The study based on an American Medicare cohort reported that the presence of AF significantly increases long-term mortality after CABG, and also the incidence of late stroke and systemic embolism.[476] A meta-analysis of 12 retrospective observational studies comparing patients with and without AF also reported that the presence of AF increased perioperative mortality, perioperative cerebral infarction, and long-term mortality by 64%, 50%, and 74%, respectively.[477] These reports endorse rigorous intervention in AF for reduction of embolic risk in patients with AF undergoing CABG.

7.3 Surgical Ablation

Surgical ablation as treatment of AF during mitral valve surgery was shown in an RCT to significantly increase the likelihood of sinus rhythm recovery.[478] Left arteriotomy is indispensable for mitral valve surgery, but not for CABG or AVR. Because of the popularity of OPCAB (without extracorporeal circulation) in Japan, the invasive burden of surgical ablation added to CABG or AVR is not considered to be comparable to that added to mitral valve surgery. However, retrospective comparative studies have shown that the addition of surgical ablation to CABG or AVR does not necessarily increase the risk. In single-center comparative studies, perioperative mortality did not differ between isolated CABG/AVR and CABG/AVR with surgical ablation.[479,480] An analysis of the Medicare population revealed no significant difference in the 90-day postoperative mortality rate between isolated CABG and CABG+surgical ablation, and also showed a lower mortality rate after 90 days for CABG+surgical ablation.[481] Additional performance of surgical ablation with CABG does not seem to increase operative mortality.

The effects of surgical ablation performed with CABG have only been investigated in observational studies without control groups, and in small comparative studies. These studies have indicated the efficacy of surgical ablation, although the reliability/usefulness of the data is limited. Damiano et al performed the Maze III procedure in 47 CABG patients (including 7 who underwent simultaneous mitral valve surgery) and reported that the rate of freedom from AF was 98% over a mean follow-up of 5.7 years.[482] Notably, multiple small RCTs have shown that pulmonary vein isolation (PVI, without the need for atriotomy) in addition to CABG can attain an outcome similar to the Maze procedure. In an RCT that assigned 95 CABG patients to PVI+CABG, mini-Maze procedure+CABG, or isolated CABG and monitored AF using an implantable loop recorder, the freedom from AF was similar between PVI and the mini-Maze procedure (80% vs. 86.2%).[483] Another RCT comparing isolated CABG with PVI+CABG in 35 patients noted a higher rate of freedom from AF for the group with PVI+CABG.[484] A study that followed 33 patients after OPCAB+PVI reported that the freedom from AF was 71% over 1 year.[485] The STS guidelines published in 2017 list the additional performance of surgical ablation to CABG for sinus rhythm recovery as a Class I recommendation.[486]

7.4 LAA Closure

LAA closure performed during cardiac surgery is common, but its benefits are not well established. A meta-analysis of data from 2 RCTs and 5 observational studies indicated LAA closure decreases perioperative cerebral infarction, long-term cerebral infarction, and all-cause death by 54%, 52%, and 62%, respectively.[487] Two retrospective observational studies based on Medicare data also showed the procedure significantly decreased cerebral infarction and all-cause death.[488,489] In a study based on another large-scale registry of CABG patients (Nationwide Impatient Sample), LAA closure decreased the incidence of cerebrovascular disease during hospital stay but increased bleedings events, pericardial effusion, and cardiac tamponade, resulting in an increased in-hospital mortality rate.[490] More data are necessary for deciding the safety of LAA closure performed with CABG.

One well-known issue with surgical LAA closure is incomplete closure resulting from surgical ligation. A transesophageal echocardiography analysis revealed the existence of residual flow in 60% of cases.[491] Significantly more frequent cerebral infarction has been reported in patients with incomplete LAA closure.[492] An epicardial LAA clip (Atriclip®) has been granted approval in Japan.

An analysis using CT reported a success rate of ≥98%.[493] An observational study involving 291 patients who underwent cardiac surgery reported cerebral infarction in only 5 (1.7%) patients during a mean follow-up of 3 years. Still, data from more reliable studies, including large-scale RCTs, are needed for the device. The benefits and safety of anticoagulation therapy after LAA closure have not been fully investigated. For Atriclip, however, the reported incidence of cerebral infarction per year in patients given aspirin without any other anticoagulants after LAA closure is 0.5%, equivalent to a relative risk reduction of 87.5% compared with the incidence predicted using CHA_2DS_2-VASc score.[493] The STS guidelines of the year 2017 list LAA closure for thromboembolism risk reduction in patients with AF undergoing cardiac surgery as a Class IIa recommendation. In this guideline, a Class IIb recommendation is given for the procedure.

VI. CABG Techniques

1. Comparison Against Medical Therapy and PCI

1.1 Treatment Effects

The true benefits of CABG can be assessed by comparing them against those of medical therapy in a RCT. All-cause death is the most objective measure of benefit. Confirmation of the benefits of CABG with a statistically significant difference against medical therapy in an RCT does not immediately translate into applicability of the procedure (i.e., whether the patient benefits from it) in the clinical setting. The number needed to treat (NNT) is one of the common measures of clinical benefit. NNT represents the number of patients needed to be treated to prevent one additional adverse event. The smaller the NNT of a treatment, the greater its clinical benefit.

In 1994, Yusuf et al published the findings of a meta-analysis of 2,649 patients with stable CAD (main trunk disease in 6.6%, proximal LAD lesion in 59.4%, 1-vessel disease in 10.2%, 2-vessel disease in 32.4%, 3-vessel disease in 50.6%, and DM in 9.6%), and reported that a survival benefit of CABG compared with medical therapy was observed with a statistically significant difference from 5 to 10 years after CABG.[133] The NNT with CABG for 5-year and 7-year survival was respectively 18 and 17, and it increased (=decreased benefit) to 24 for 10-year survival. Evidence supports the survival benefit of CABG and continued listing as a Class I recommendation for CABG in stable CAD, despite recent advances and development of more aggressive medical therapy and PCI. The report by Yusuf et al has been challenged by later studies. For instance, some have thrown doubt on the benefit of CABG itself, arguing that statin therapy was not in use at the time of the report and that today's CABG does not have the reported survival benefit. On the other hand, others have argued that the observed decrease in benefit after 7 years was due to the use of venous graft alone in most (90%) of the patients and that, because the ITA rather than venous graft is most commonly used today, the survival benefit of today's CABG is even longer.[494]

The MASS II study,[495] STICH study,[212] and BARI 2D study[183] are some of the RCTs that have compared CABG against medical therapy after the spread of statin therapy and ITA graft use. The MASS II study was conducted in a small number of patients who had relatively simple, low-risk disease without main trunk lesions and who were free of impaired cardiac function (42% had 2-vessel disease and 58% had 3-vessel disease). The study found no significant difference over 5-year follow-up. After 10 years, however, the incidence of cardiac death was 20.7% for medical therapy vs. 10.8% for CABG (P=0.019). The incidence of myocardial infarction was respectively 20.7% and 10.3% (P=0.010).[495] The STICH study compared medical therapy (602 patients) with CABG (610 patients) among those with stable CAD complicated by impaired cardiac function (LVEF ≤35%). The study reported no significant difference after 5-year follow-up. After 10 years, however, the all-cause mortality rate was 66.1% for medical therapy vs. 58.9% for CABG (P=0.02). The NNT with CABG for 10-year survival was 14.[212] The BARI 2D study (in 763 patients with DM) administered potent lipid-lowering therapy. In this setting, CABG decreased the incidence of myocardial infarction in the 5-year follow-up (17.6% in aggressive medical therapy group and 10.0% in CABG group). The NNT with CABG for prevention of secondary myocardial infarction in 5 years was 13.[183]

The aforementioned reports show that CABG using ITA grafts can improve survival and reduce secondary myocardial infarction (level of evidence=A), even in patients on aggressive medical therapy, for longer than 10 years. Due to advances in medical therapy, however, the length of time needed for CABG to demonstrate its benefits superior to medical therapy is probably longer now, especially for the treatment of simple lesions, than when the study by Yusuf et al. was conducted (**Table 30**).

1.2 2-/3-Vessel Disease With Diabetes

The CREDO-Kyoto registry is the only Japanese prospective cohort study comparing CABG and PCI. According to a report based on the registry, the 3-year mortality rate with PCI (using BMS) in 2- and 3-vessel disease patients (n=5,420) was significantly higher compared with CABG in the group with DM rather than among patients with 3-vessel disease (adjusted hazard ratio [HR], 1.38; P=0.003).[496] In another report on patients with 2-vessel disease, 3-vessel disease, or main trunk lesion (n=3,982),

Table 30. Conditions Favoring Coronary Artery Bypass Grafting

- Presence of diabetes mellitus
- Impaired cardiac function (LVEF ≤35%)
- Multivessel disease or main trunk lesion with SYNTAX score ≥23

LVEF, left ventricular ejection fraction.

based on the same registry, the 5-year mortality rate was similar between PCI (using DES) and CABG among non-DM patients but was higher for PCI (adjusted HR, 1.31; P=0.04) among DM patients.[497]

Head et al. contacted the principal investigators of 11 RCTs in patients with 2-vessel, 3-vessel, or main trunk lesions, and analyzed data of a total 11,518 patients enrolled in those trials and published the results on the *Lancet's* website on February 22, 2018.[173] The mean follow-up period was 3.8 years across the trials. The 5-year mortality rate was 9.2% for CABG and 11.2% for PCI (P=0.0038). The NNT with CABT for 5-year survival was 50, which is not impressive. In a subgroup analysis, quantitative interaction was observed only with DM. In 2- and 3-vessel disease patients with DM, the 5-year mortality rate was 10.0% for CABG and 15.5% for PCI (P=0.00037). The NNT with CABG for 5-year survival was 18. In non-DM patients, survival benefit was similar between CABG and PCI. SYNTAX score revealed no interaction, but a higher score tended to be associated with a greater survival benefit of CABG.

2. Preoperative Management

2.1 Performance Status

Apart from preoperative coronary angiography, evaluating the patient's baseline performance status, including organ function, arteriosclerotic lesions, and severity of comorbidities other than cardiac function (e.g., myocardial viability, valvular disease), should help obtain useful information for choosing a suitable CABG technique to minimize postoperative complications and also for intraoperative and postoperative management. The patient's baseline comorbidities should also be evaluated individually to decide whether CABG can be performed safely.

- Hematology: Anemia, renal/hepatic function tests, infection, DM, fibrinolytic system, thyroid function, electrolytes, and any other tests necessary for evaluation of existing diseases/conditions.
- CT: Head imaging for brain disorders, including assessment of the severity of asymptomatic cerebral infarction, etc.
  Chest imaging to evaluate aortic arteriosclerosis and to collect information relevant to selection of surgical technique (e.g., on-pump or off-pump, side-bite clamp or clampless devices for proximal anastomosis).
  Abdominal imaging from the abdominal aorta through the iliac and femoral arteries to detect aneurysm and arteriosclerotic obliteration and check out whether IABP or PCPS cannula can be inserted via a femoral artery.
- Echocardiography: Useful for evaluation of cardiac function, left ventricular dilatation, valvular disease, and the area of myocardial ischemia.
- MRI: Cardiac MRI allows accurate assessment of left ventricular function. Delayed enhancement MRI is used in cardiac viability assessment.
- Myocardial scintigraphy: Useful in myocardial viability assessment.
- Carotid ultrasonography: To visualize stenosis and mobile plaque inside the carotid artery and predict perioperative cerebrovascular complications.
- Respiratory function test: To assess the risk of obstructive pulmonary disorders.

2.2 DM

CABG has been reported to be more effective than PCI in patients with DM.[498] However, DM is not only associated with survival and cardiovascular complications after CABG, but is also a risk factor of postoperative infections/respiratory complications and prolonged hospital stay. HbA1c ≥6.5% (or ≥7.0% in some reports) has been repeatedly reported to be a strong risk factor of surgical site infection (SSI) and sternal wound infection,[499–501] indicating HbA1c <6.5% should be a reference point for baseline diabetic management. HbA1c represents the level of glycemic control 2–3 months before the measurement. For many patients who require CABG, waiting for HbA1c to drop to a suitable level is not feasible. There is a report of 2-week preoperative glycemic control sufficiently decreasing postoperative infections. In patients with high HbA1c levels who need to undergo CABG, perioperative glycemic control is essential for control of perioperative SSI and sternal wound infection.[502,503]

For patients with diabetic retinopathy, however, an excessive decrease in HbA1c with aggressive insulin therapy can worsen the retinopathy.

2.3 Preoperative Anticoagulation/Antithrombotic Therapy

Anticoagulation/antiplatelet therapy in the perioperative period of CABG is given as care for preoperative angina and also effective for decreasing the risks of early graft occlusion and embolism due to increased postoperative platelet activity. At the same time, however, they can increase perioperative bleeding and blood transfusion requirements.[504] Among various anticoagulants/antiplatelets, low-dose aspirin is recommended through the perioperative period of CABG because it may lower the incidence of acute graft occlusion without significantly increasing bleeding risk.[505] When clopidogrel is used, bleeding risk is thought to increase 20% with clopidogrel alone and 50% when clopidogrel+another antiplatelet drug are administered. For risk control, clopidogrel should be stopped 5–10 days before CABG while continuing with aspirin.[506,507]

Recently, oral prasugrel has been used for possible emergency PCI. The time to onset of action of prasugrel is only a few hours, which is convenient when emergency PCI becomes necessary. However, if emergency CABG is performed, prasugrel will start to exert its action at the time of surgery and increase bleeding risk. Platelet transfusion should be kept ready for control of bleeding during emergency CABG.

2.4 Emergency/Urgent CABG

Maintenance of stable hemodynamics is of utmost importance in the preoperative period of emergency or urgent CABG. IABP is the preferred procedure. Keeping BP high to minimize myocardial infarction and progression of myocardial ischemia is important for early postoperative recovery. When the patient has recurrent ventricular arrhythmia or presents with low BP, there should be no hesitation in using percutaneous cardiopulmonary support, which can decrease the risks associated with anesthesia.

2.5 HF

Emergency or urgent CABG is often performed in patients with acute HF as a result of acute myocardial infarction and/or myocardial ischemia. If the patient also has severe pulmonary congestion, it is reasonable to provide care for HF for a few days before CABG. Resolution of ischemia is the key for care of HF in such patients. A minimum level of coronary circulation should be restored by, for instance, plain old balloon angioplasty (POBA) for early recanalization. When coronary artery anatomy is not amenable to PCI and myocardial ischemia persists, CABG should be chosen even if HF is severe.[64]

3. Blood Management

3.1 Blood-Saving Strategies (Table 31)

An automated autologous blood collection/transfusion system was useful for reducing intraoperative bleeding and blood transfusion in a number of reports, and is used widely in CABG or OPCAB (excluding in patients in whom the system is contraindicated).[508–510] The system can decrease the systemic inflammatory response, allow fat removal, and does not increase the risk of infection.[511–513]

CABG without cardiopulmonary bypass (OPCAB) reduces bleeding compared with CABG with cardiopulmonary bypass (ONCAB)[514,515] and can be an option when the risk of graft occlusion and conversion to cardiopulmonary bypass is low.

A cardiopulmonary bypass circuit with low-volume priming achieved by eliminating the open venous reservoir (closed circuit) is designed to reduce blood dilution/transfusion and to minimize blood–air contact for lower inflammatory response risk compared with conventional cardiopulmonary bypass devices. The efficacy of closed circuits for blood-saving has been demonstrated by many RCTs and is commonly accepted.[516–519] A closed circuit is especially useful when cardiopulmonary bypass becomes necessary in patients who refuse blood transfusion (for religious reasons, etc.).[520,521]

Reports published in the 1980s documented the efficacy of applying positive end expiratory pressure (PEEP) 5–20 cmH_2O for hemostasis in patients with ≥200 mL/h bleeding from the drain.[522,523] Though there are not much data supporting efficacy, PEEP may be worth trying in patients with significant postoperative bleeding. Prospective studies have noted that routine use of PEEP regardless of the amount of bleeding does not help decrease bleeding and is not recommended.[524–526]

Table 31. Recommendation and Evidence for Blood-Saving During Coronary Artery Bypass Grafting

	COR	LOE
Intraoperative use of an automated autologous blood collection/transfusion system (Cell Saver) to reduce transfusion (excluding patients with malignancies/infections)	I	A
Use of a closed circuit, when cardiopulmonary bypass is used, to reduce blood dilution and transfusion	I	A
OPCAB for reduction of blood loss/transfusion when it is not likely to cause conversion to cardiopulmonary bypass or risk bypass occlusion	IIa	A
Use of PEEP for hemostasis in a patient with significant bleeding from the drain	IIb	B
Routine use of high PEEP to control hemorrhage from the drain	III	B

COR, class of recommendation; LOE, level of evidence; OPCAB, off-pump coronary artery bypass; PEEP, positive end expiratory pressure.

Table 32. Recommendation and Evidence for Use of Blood-Saving Agents in CABG

	COR	LOE
Stop antiplatelet drugs, excluding aspirin, to minimize the risk of postoperative bleeding (if the patient is continuing DAPT)	I	B
Administration of lysine analogs (e.g., tranexamic acid) to reduce bleeding after CABG	I	A
Administration of aprotinin to reduce bleeding after CABG	III	A

CABG, coronary artery bypass grafting; COR, class of recommendation; DAPT, dual antiplatelet treatment; LOE, level of evidence.

3.2 Pharmacological Approach (Table 32)

In Japan, erythropoietin use is covered by National Health Insurance only in preoperative autologous blood donation. Preoperative administration of erythropoietin with iron preparation without autologous blood donation is therefore not covered by insurance, although it is recommended elsewhere for patients with preoperative anemia or who refuse blood transfusion.[527] A meta-analysis of data from patients with preoperative anemia reported that preoperative erythropoietin+iron preparation significantly decreased postoperative homologous blood transfusion regardless of being with/without autologous blood donation.[528]

Whether in OPCAB or ONCAB, preoperative oral aspirin+clopidogrel increases postoperative bleeding and blood transfusion and therefore is not recommended.[529,530] A meta-analysis also indicated that DAPT administered within 5 days before CABG significantly increased the incidence of reoperation for bleeding and death while not affecting the incidence of perioperative myocardial infarction or major adverse cardiac events (MACE).[531]

Aprotinin used to be regarded as useful for postoperative hemostasis, but is no longer recommended because of reports showing that it increased the perioperative mortality rate significantly compared with lysine analogs (tranexamic acid, aminocaproic acid).[532–535] Lysine analogs have a potent hemostatic effect with relatively few adverse reactions and are recommended.[535,536]

3.3 Blood Transfusion (Table 33)

At what level of anemia RBC transfusion should be given during or after CABG is a very important question that resists a generalized answer. EU/US guidelines indicate RBC transfusion is absolutely required at Hb 6 g/dL and is reasonable to consider at ≤7 g/dL.[527] Hb 6 g/dL is considered the minimum required for safe transport of oxygen.[537,538] In patients who are indicated for CABG/OPCAB, 7 g/dL is regarded as the minimum instead.[539] In a recent RCT,

Table 33. Recommendation and Evidence for Blood Transfusion During Coronary Artery Bypass Grafting

	COR	LOE
RBC transfusion in patients with Hb ≤7 g/dL	I	C
RBC transfusion in patients with Hb >7 g/dL and ≤9 g/dL	IIa	C
RBC transfusion in patients at risk of cerebral ischemia, aged patients, or patients with impaired cardiac function	IIa	C
Use of fresh frozen plasma for control of bleeding in patients without coagulation disorders	III	A

COR, class of recommendation; Hb, hemoglobin; LOE, level of evidence; RBC, red blood cells.

Table 34. Recommendation and Evidence for LITA Graft

	COR	LOE
LITA-to-LAD bypass grafting	I	B
Bypass grafting of circumflex branch using LITA graft	IIa	B
Skeletonization of LITA graft for graft extension or increased graft flow	IIa	B
Skeletonization of LITA graft to avoid mediastinitis	IIa	A

COR, class of recommendation; LAD, left anterior descending coronary artery; LITA, left internal thoracic artery; LOE, level of evidence.

5,243 patients were treated with cardiotomy and transfusion at Hb 7.5 g/dL or at 9.5 g/dL and no significant difference in perioperative deaths between the groups was reported, suggesting an Hb of about 7.5 g/dL is an adequate threshold.[540] In a guideline published by the Japan Society of Transfusion Medicine and Cell Therapy, however, 9–10 g/dL is stated as the optimal Hb range after cardiac surgery.[541] The guideline supports the 9–10 g/dL range by citing reports, including a meta-analysis, noting that patients with 9–10 g/dL of Hb have a significantly lower mortality rate compared with patients with lower Hb levels.[542–545]

There are fewer reports on appropriate hematocrit levels. Wu et al. reported a significantly lower mortality rate in patients given blood transfusion than in others not given blood transfusion among patients aged ≥65 years who were hospitalized with acute myocardial infarction and had ≤30% hematocrit.[546]

Prophylactic use of fresh frozen plasma is not recommended because numerous reports have shown it does not affect bleeding after cardiac surgery.[547–550]

4. Vessel Harvesting

4.1 LITA (Table 34)

LAD revascularization using a LITA graft (LITA–LAD), compared with revascularization with a venous graft, maintains better short-term and long-term patency and has higher survival and cardiac event-free rates.[551–560] Venous graft patency decreases after 5 years, but LITA grafts maintain ≥90% patency[551] with notably higher survival and cardiac event-free rates than venous grafts for over 10–20 years.[552,553] In Japan, there is one report showing favorable outcomes of LITA–LAD at 10 years after surgery.[554] For CABG in the LAD, evidence indicates the LITA graft is the definitive first choice. Although some reports have indicated that the use of a right ITA (RITA) graft in CABG on the LAD (RITA–LAD) achieves similar outcomes to LITA–LAD,[561–563] no grafts have been reported with better outcomes than the LITA. LITA–LAD is considered the gold standard in CABG.

However, few studies have reported the outcomes of CABG with LITA grafts used in vessels other than the LAD.[561,564] In a study of CABG with LITA grafts in 1,482 patients, graft patency was 97.2% with LITA–LAD after a mean of 79 months compared with 91.0% with LITA to the LCX, suggesting that anastomosis of a LITA graft to the LCX constitutes a risk factor of LITA graft occlusion.[561] Combining the LITA with RITA–LAD is recognized as an effective approach when the LITA is to be grafted to a non-LAD artery such as the LCX.[564]

Skeletonization is now recommended as a standard procedure for LITA harvesting.[139] In a study of 200 consecutive patients, skeletonized LITA grafts were on average 4 cm longer and had 30% greater flow and attained an early patency rate of 99.6%.[565] Skeletonization is also considered an effective technique for prevention of mediastinitis compared with the more traditional harvesting of LITA as a pedicle.[566–569] The risks of graft injury and vasoreactivity have been the greatest concerns raised for skeletonization, but they have been shown to be similar between skeletonization and harvesting as a pedicle.[570] In particular, the safety of the harvesting procedure using the harmonic scalpel is widely accepted.[571,572] Using a skeletonized LITA as a sequential bypass graft in the LCX has been noted to improve the outcomes of CABG.[573,574] Sequential bypass grafting is expected to become an important procedure with the expected diversification of arterial graft usage. Because of this, the skeletonized LITA will prove extremely valuable for safe and longer graft length.

4.2 RITA (Table 35)

Due to the favorable outcomes of CABG with LITA graft, the use of the BITA graft has gained popularity. In a retrospective study of medium- to long-term outcome, BITA lowered the mortality rate and decreased other events in both young adults[575–585] and aged individuals.[586–589] Also, the superior survival benefit of BITA compared with either LITA or RITA has been shown to grow for over 20 years after CABG.[590]

For CABG, recent studies show that RITA–LAD can achieve similar outcomes to LITA–LAD,[591,592] and postoperative graft patency is similar between them.[554,593,594] The outcome of CABG with RITA grafted to the LCX is also similar to that for LITA–LAD.[593,595–597] However, RITA grafted to the RCA, although limited numbers among the reported cases, has shown a relatively low patency of about 80% with a high postoperative event rate.[561,587,598,599] RITA grafting to the LCA in BITA operations reportedly achieves better survival than grafting to the RCA.[575]

As diverse arterial grafts come into use, RITA is increas-

Table 35. Recommendation and Evidence for BITA/RITA Graft

	COR	LOE
Use BITA graft to decrease mortality and other events in the long run	IIa	B
Choose left coronary artery region for anastomosis of in situ RITA graft	IIa	B
Skeletonization of BITA graft to reduce the risk of mediastinitis	IIa	B
LAD bypass grafting with RITA	IIb	B

BITA, bilateral internal thoracic artery; COR, class of recommendation; LAD, left anterior descending coronary artery; LOE, level of evidence; RITA, right internal thoracic artery.

Table 36. Recommendation and Evidence for GEA Graft

	COR	LOE
RCA bypass with right GEA graft	IIa	B
RCA bypass using right GEA or SV graft to achieve long-term survival	IIa	B
Bypass grafting using right GEA for severe RCA stenosis	IIa	C
Skeletonization of right GEA graft to reduce spasm	IIb	C

COR, class of recommendation; GEA, gastroepiploic artery; LOE, level of evidence; RCA, right coronary artery; SV, saphenous vein.

ingly used as a free graft. For proximal graft anastomosis, RITA is used as a composite graft with LITA,[600–605] other than anastomosed to the ascending aorta.[561,606] Higher patency and improved graft length have been reported for such use. There is also a report contending that the BITA graft configuration has no effect on survival.[607] No consensus has been reached about whether BITA should be used in situ or as a composite.

Mediastinitis is one of the potential postoperative complications in CABG with BITA. Patients with DM (especially obese women)[310,608–610] or with chronic obstructive lung disease[561,593–605] are known to be at risk of mediastinitis. The skeletonized ITA decreased mediastinitis according to some reports.[310,569,611–614] However, the incidence of postoperative mediastinitis is similar between skeletonization of BITA and SITA.[615]

4.3 GEA (Table 36)

The first use of the right GEA as the 3rd type of in situ arterial graft for CABG was reported in 1987.[616,617] Although an in situ GEA graft can be anastomosed to any segment, it is most commonly used in the RCA. There is no systematic report on the long-term outcomes of GEA grafts by target coronary artery. Available data on early and long-term outcomes are mostly from reports of GEA grafts anastomosed to the RCA. The early postoperative patency ranges from 88% to 100% in such reports.[578,618–636] Notable long-term (≥3 years) patency is 91.1–96.0% for 3 years,[629,636] 80.5–94.7% for 5 years,[624,627,629] and 62.5–66.5% for 10 years.[627,634]

With bypass grafting to the RCA, the 5-year patency of RITA is 83% according to a study.[637] Some researchers are against RITA grafting to the distal segment of the RCA and its branches.[638] Comparison between RITA and GEA use for the RCA is controversial. The 5-year patency rate of RA grafts is 73–83%,[637,639,640] which is similar to that for GEA. The superiority of GEA to SVGs in 5-year patency rates has been noted.[624] The 10-year patency rate of saphenous vein (SV) grafted to the RCA is 56% according to a report;[294] however, a slightly higher 10-year patency rate of SV compared with GEA graft was shown in another report.[627] There are still others noting that the GEA has no specific clinical benefit,[642,643] and there are disagreements also about the long-term outcome of GEA vs. SVGs.

The degree of stenosis of the coronary artery affects the patency of the GEA. It is the 3rd branch of the abdominal aorta and has a BP 10–15 mmHg lower than in the ITA. Because of this, the GEA graft is sensitive to competitive flow with the coronary artery when the coronary artery has moderate stenosis. Competitive flow can decrease the shear stress of GEA, reduce vasoactive substances such as nitric oxide, and increase the risk of graft failure.[644,645] When the target coronary artery has severe stenosis, however, competitive flow is unlikely to develop. The GEA maintains good function and a smooth lumen with a high patency rate in that case.[624,636,646]

Unlike the ITA, the GEA is contractile and prone to vasospasm. However, skeletonization using the harmonic scalpel can safely reduce spasm, extend the graft length, and enable anastomosis with a larger diameter vessel.[647–649] Removing the periarterial nerve of the GEA can also further lower the risk of vasospasm, and removal of periarterial connective tissues by skeletonization may also achieve denervation.[650] In addition, skeletonization of the GEA can help avoid competitive flow and improve long-term graft patency.[634–636,651] There is still disagreement about the GEA's utility as the inflow of a composite graft,[621,652–655] and of its patency when used as a free graft.[628,656,657]

4.4 RA (Table 37)

4.4.1 RA Graft Uses and Advantages

The RA is often used as the 2nd/3rd arterial graft (the 1st being the ITA) chosen (e.g., for complete revascularization) in multivessel disease. The RA can be used in aorto-coronary (AC) bypass or as composite graft with the ITA and increase the applicability of CABG.[658,659] When used as a composite graft, the RA makes off-pump surgery easier and enables aortic no-touch bypass grafting. A meta-analysis has shown that the aortic no-touch technique decreases the incidence of cerebral infarction significantly compared with CABG under cardiopulmonary bypass or

Table 37. Recommendation and Evidence for RA Graft

	COR	LOE
Use of RA as the 2nd graft to the LITA for bypass of severe LAD stenosis	IIa	B
Use of RA as aorto-coronary bypass or as composite graft and sequential anastomosis	IIa	C
Medical therapy with RA graft for reduction of spasm	IIa	B

COR, class of recommendation; LAD, left anterior descending coronary artery; LITA, left internal thoracic artery; LOE, level of evidence; RA, radial artery.

Table 38. Recommendation and Evidence for SV Graft		
	COR	LOE
Endoscopic SV harvesting for less wound complications and infections	IIa	A

COR, class of recommendation; LOE, level of evidence; SV, saphenous vein.

OPCAB that touches the aorta. Other cardiac complications are also less frequent with the no-touch technique.[660] Unlike the ITA, RA graft harvesting is free from complications associated with midline incision (e.g., mediastinitis).

As RA graft usage spreads, more favorable data are being published. The RA graft is now chosen as the 2nd arterial graft in some cases. Clinicians planning to use the RA should note that the long-term outcomes of CABG with the RA can vary by the level of stenosis in the target vessel and that the RA requires premedication to prevent vasospasm.

4.4.2 Vessel Harvesting

The RA is 1 of the 2 continuations of the brachial artery (the other being the ulnar artery) and runs along the radius. Whether or not ischemia in the palm can be avoided mostly determines whether an RA graft can be harvested. The Allen test and Doppler ultrasonography should be performed for characterization of the artery. Also, the RA's position relative to the ulnar artery in the palm needs to be checked.[661–663] The skin incision for RA harvesting is made from the elbow to the wrist. The lateral forearm cutaneous nerve and superficial radial nerve must be carefully avoided. Endoscopically harvested RA graft has been reported to have similar patency compared with grafts harvested by open surgery, but with reduced surgical wound pain and numbness.[664–668]

4.4.3 Medication

Medication may be given (1) to the RA graft or (2) to the patient after CABG. Compared with the ITA, the RA has more smooth muscle and is prone to vasospasm. The harvested RA should be promptly immersed in a vasodilator solution.[669–673] Commonly, a papaverine hydrochloride solution, milrinone, or verapamil-nitroglycerine (VG) solution is used. According to the literature, the VG solution is the most effective.[669–673] Typical perioperative medication is intravenous calcium antagonist, switched to oral administration when the patient is able to swallow and continued for an extended period.[674]

4.4.4 Usage and Outcome

Many RCTs and meta-analyses indicate the patency of RA grafts is similar to that of the SV in the short term because some patients have the string sign on the RA. In the long term, however, RA grafts have shown significantly higher patency than the SV.[675–683] The string sign is diffuse narrowing along the full (or most of) length of the graft or localized spasm and is reported in up to 7% of patients.[675] Recent RCTs show that the long-term patency rate of RA grafts is much higher than with the SV and similar to the ITA.[684] To achieve long-term patency of an anastomosis with the RA, however, the degree of proximal stenosis in the target coronary artery must be ≥90%.[658,659,684] If the degree of stenosis is <90%, competitive flow tends to develop and decreases the long-term patency to about the same as that of the SV.[684] In older (age ≥75 or ≥78 years) patients, the superiority of the RA over the SV may not exist,[684,685] making patient age an important factor in graft selection.

When LITA–LAD is chosen as the primary technique, either the RITA or RA is commonly chosen as the 2nd arterial graft. Although no large-scale study has compared these grafts, patency rates seem to be similar or slightly better for the RITA.[678,686–688] However, RA harvesting carries no risk of mediastinitis and should be more suitable for aged individuals and patients with DM.[684,689] The use of the RA with BITA can improve survival without increasing operative risk, and regardless of sex and whether or not the patient has DM,[690] and is therefore an option worth considering.

4.4.5 Graft Design

The RA can be used as a composite graft and therefore can be used in sequential anastomoses. Some reports note that the RA used in AC bypass attains higher short- and long-term patency than when used as a composite graft, but others contend the patency rate is similar between such uses.[640,691–695] Also, some studies reported a higher patency rate with sequential anastomoses than with single anastomosis; however, similar patency rates were noted by others.[696–698] The available evidence therefore seems to suggest no significant difference between the inflow to RA graft being the aorta or the ITA. There are reports indicating that increased anastomoses do not affect patency, suggesting greater potential graft and design choices when complete revascularization is the goal.[658,659,695–697]

4.5 SV (Table 38)

4.5.1 Effect of Different Harvesting Techniques

The SV is still an important graft option for CABG. It can be harvested by open or endoscopic techniques, and there is also a new "no-touch SVG" (NT-SVG) method whereby the SV is harvested with a pedicle of surrounding fat.

Subgroup analysis in the PREVENT IV study reported that different harvesting techniques of the SVG may affect the outcome of CABG.[699] Endoscopically harvested SVGs were associated with significantly lower graft patency compared with grafts harvested by open techniques. Also, the incidence of myocardial infarction, long-term repeat revascularization, and long-term mortality were higher for CABG performed using endoscopically harvested SVGs. However, criticisms were raised about inconsistent skills among the surgeons who harvested the grafts and also about potential biases in the study. More RCTs and multicenter studies were conducted subsequently,[700–703] and today's consensus is that endoscopically harvested SVGs do not have inferior clinical outcomes compared with grafts harvested by open techniques. Nevertheless, the learning curve of the endoscopic harvesting technique does affect graft quality.[704] An inexperienced surgeon can cause damage by excessive pulling, heating by electrocautery, or tears at branch points. Also, more endothelial damage was noted with the endoscopically harvested SV compared with the SV harvested by open techniques.[705,706]

The biggest advantages of endoscopic harvesting are patient preference and reduced surgical site infection. Some RCTs reported endoscopic SV harvesting can reduce infection at the site of harvest,[707–709] and a multicenter

study has shown that harvest site infection notably prolongs hospital stay.[710] Because of this, in the USA where prolongation of hospital stay caused by surgical site infection has a significant effect on hospital costs, endoscopic harvesting is used in 70% of all CABG cases with SVGs.[155,707,709] The ESC/EACTS guidelines for 2014 describe endoscopic SV harvest reducing surgical site infection and list it as a Class IIa recommendation.[139]

Endoscopic SV harvest is therefore a favored technique due to its association with less surgical wound problems, but more time is needed for the overall evaluation of the outcomes of CABG with endoscopically harvested SVGs (e.g., long-term graft patency).

4.5.2 NT-SVG

NT-SVG harvesting is an open technique that began in the 1990s.[711] NT-SVG harvesting removes the SV with surrounding fat as a pedicle and does not require dilatation by syringe.

A recent RCT reported that the patency of the NT-SVG after 16 years was 83%, which is significantly higher than that with SVGs harvested by other techniques and is close to the 88% reported for LITA grafts.[712] Clinical outcomes of the NT-SVG have also been reported in a subgroup analysis of the SAVE-RITA study. That analysis showed that the early and 1-year patency rates of the NT-SVG were 100% and 97.4%, respectively, both of which are significantly higher than those of SVGs harvested by other techniques.[713]

Because the NT-SVG is not dilated by syringe, the endothelium and venous wall are undamaged and are not excessively dilated. The SVG is commonly anastomosed to the aorta. The endothelial cells of the graft are damaged to some extent by exposure to arterial pressure, but intraluminal dilation by syringe can significantly increase the loss of endothelial cells.[714] Many reports support the pathological and physiological benefits of the NT-SVG.[715–719] Preservation of the vasa vasorum around the SV helps maintain blood flow in the venous wall and may contribute to long-term graft patency.[720–723]

The long time required for cure at the harvest site is a concern with the NT-SVG. Using an interrupted skin incision and drain tube, however, will likely make the incidence of surgical site complications similar to that with conventional techniques.[713] The frequency of abnormal cutaneous sensation is reportedly similar between NT-SVG harvesting and conventional techniques at 1 year after harvesting.[724] The reported benefit of the NT-SVG in long-term patency is not well established because the graft has so far been used in only a limited number of institutions.

4.5.3 Effect of Different Harvest Sites

The SV is harvested from the femur or lower leg, and whether either site attains higher patency has not been determined. Normally, the SV in the lower leg is thinner than in the femur. The caliber of an SVG may be related to its patency. A study that followed the patency of SVGs for over 20 years noted the frequency of occlusion was higher for SVGs with a larger caliber at the time of surgery.[725] Subgroup analysis of the CASCADE study also reported that the degree of SV intimal thickening at 1 year after CABG was significantly more severe for the thicker SV.[726]

These findings suggest an SVG should be preferably harvested from the lower leg where the vein is thinner.

4.5.4 External Stent

Attempts have recently been made with placement of a metal external stent around the SVG to improve patency.[727,728] External stent placement can protect the SVG from excess dilation, correct intraluminal irregularities, and mitigate size mismatch between the coronary artery and SVG. Intravascular ultrasound (IVUS) revealed less intimal thickening inside an SVG at 1 year after external stent placement.[729,730]

The idea of external stent placement is over 50 years old,[731] but its clinical application only began recently with SVGs in CABG. The early clinical results of external stenting were poor at best, with reported early postoperative patency rates of 0–34%.[732–734] The patency rate of external stenting has improved with the development of new stents with different shapes and materials, but still remains unsatisfactory.

5. Diffuse Stenosis

5.1 Significance of Revascularization and On-Lay Patch Grafting

Against the background of increasing arteriosclerotic disease among rapidly aging populations, CAD is diversifying and becoming more complex. In addition to multivessel disease and LMCA disease, some patients present with diffuse stenosis in distal segments.

Diffuse stenosis may require placement of multiple stents, but severe calcification can prevent stent insertion, making catheterization difficult. Tsagalou et al reported perioperative myocardial infarction in 16.6% of patients who had a stent implanted over long lesions, and restenosis within 6 months in 19.6%.[735] Sharp et al inserted a stent into the site of long (≥60 mm) lesions in 617 patients using the full-metal jacket procedure, and observed cardiac death in 3.6% and perioperative myocardial infarction in 9.5% over a mean follow-up of 38.9 months, and reported a TLR rate of 23.4% over the same period.[736] Shirai et al. also reported the TLR rate tended to increase for the longer lesions.[737] For long lesions, stent implantation is showng a higher incidence of perioperative myocardial infarction and TLR. In particular, occlusion of side branches by a stent implanted in a long LAD lesion is most problematic.

Surgery for diffuse stenosis also involves difficulties. Because of the poor vascular condition, conventional anastomosis may not be applicable. Even when anastomosis to the distal side is feasible, sometimes only partial revascularization is achievable in the side branches. Because incomplete revascularization in the LAD is thought to significantly affect treatment outcomes,[738] maintaining sufficient blood flow is crucial.

On-lay patch grafting is a technique indicated for CABG in diffuse stenosis.[739–741] It involves making a longitudinal incision into the diffusely stenotic segment and subsequent anastomosis of the segment with a graft cut open for the same length. The arteriosclerotic lesion at the stenotic site is placed outside by anastomosis, leaving the normal intima of the graft to cover most of the lumen. On-lay patch grafting allows observation inside the lumen of the side branches, which helps achieve complete revascularization. Endarterectomy is added when the intimal condition is particularly poor. Endarterectomy was first started in the 1950s and initially had poor results,[742–744] but the procedure has

evolved and is now applied to more complex lesions with better results.

5.2 Indication of On-Lay Patch Grafting

The primary goal of on-lay patch grafting in diffuse LAD stenosis is to revascularize the side branches occluded by the diffuse stenosis, together with revascularization of the distal arteries. Even when a graft can be anastomosed to the distal side of a diffuse lesion, the stenosis on the proximal side may block adequate recovery of blood flow in the side branches (especially in the diagonal or septal branch of the LAD). Revascularization of a long segment including side branches is required in such cases. On-lay patch grafting is intended for patients who require a long anastomosis of the graft to revascularize affected side branches.

It is also suitable when multiple lesions are spread over distal segments of the coronary artery and where anastomosing a graft at a point proximal to the more distal lesions would leave distal stenoses. When calcification in the distal segments makes normal anastomosis difficult, on-lay patch grafting with endarterectomy is called for as the final option. Patients with such lesions often have an old anteroseptal myocardial infarction and require preoperative evaluation of myocardial viability in the LAD territory using myocardial scintigraphy, MRI, and/or ultrasound cardiography. On-lay patch grafting has little clinical relevance when the patient has poor myocardial viability and revascularization is unlikely to reverse the ischemia.

5.3 On-Lay Patch Grafting Procedure

5.3.1 Target Vessels and Graft

On-lay patch grafting primarily involves longitudinal dissection of an artery with diffuse stenosis and anastomosis of a graft over the dissection.

The LAD is the most common target of this technique among the coronary arteries, because of the sheer number of vessels that branch out from the LAD and the large area of myocardium perfused by the LAD and its branches. The ITA graft is used for on-lay patch grafting to the LAD. Arteries in general have better patency rate than veins when used as bypass grafts. In particular, the ITA graft has a 10-year patency rate >90% and is regarded as the best conduit.[552] ITA grafting to the LAD improves survival. On-lay patch grafting is thought to have a similar benefit. For the ITA graft, skeletonization is preferred for harvesting a long and thick graft that is suitable for extensive anastomosis.

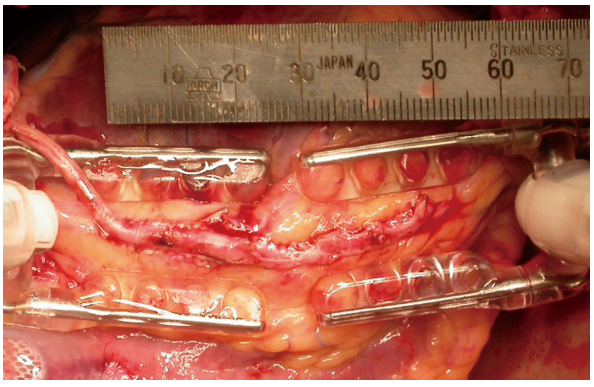


Figure 4. Diffusely stenosed left anterior descending coronary artery grafted longitudinally with left internal thoracic artery.

5.3.2 On-Lay Patch Grafting

On-lay patch grafting (**Figure 4**) involves opening the target vessel over the entire diffuse lesion and reconstruction of the vessel without removal of arteriosclerotic intima.[740] The dissection is made in the distal direction until the point where almost normal intima is observed. The graft is cut open for the same length and anastomosed to the dissected vessel. Anastomosis uses 8-0 or 7-0 polypropylene sutures. Suturing must be done with care not to block the ostia of the side branches. The length of the dissection/anastomosis is 2–10 cm.

The key to this technique is positioning of the arteriosclerotic lesion to the outside of the suture line. This leaves little lesion inside the lumen formed by the anastomosed graft, which is necessary for long-term patency.

5.3.3 Endarterectomy

The oldest endarterectomy procedure from 1950s is the closed method in which the intima is pulled out from a coronary artery incision. The patency rate with this method is poor, and it is no longer used in many institutions. On the other hand, in open endarterectomy, a longitudinal incision is made for separation and removal of the intima followed by reconstruction of the vessel using a graft cut open for the same length. Open endarterectomy achieves a higher patency rate than the closed method. Open endarterectomy is founded on the same idea as on-lay patch grafting.[740] The normal intima of the graft covers most of the inside of the reconstructed vessel.

Open endarterectomy is built on the on-lay patch grafting procedure and used in patients with severely thickened intima. The plaque is removed to the distal extremity (**Figure 5**) until the point where almost normal intima is observed. The posterior intima at the distal end of the endarterectomy incision is anchored to the adventitia by suture. The intimal flaps remaining on the adventitia are removed carefully with rinsing.

5.3.4 Postoperative Anticoagulation Therapy

Postoperative anticoagulation therapy is critically important with on-lay patch grafting. When endarterectomy is performed simultaneously, the risk of thrombus formation is particularly high. Prompt anticoagulation therapy is necessary to reduce the risk of early thrombotic occlusion. Intravenous heparin is started once postoperative bleeding has been controlled and is switched to oral antiplatelets and warfarin when the patient is capable of awallowing.

5.4 Outcome of On-Lay Patch Grafting

Because of the controlled risk of early thrombotic occlusion, on-lay patch grafting has been reported with favorable results, including patency rate. Barra et al used the ITA in on-lay patch grafting to the LAD and reported a patency rate of 95%.[739] Fukui et al also had a patency rate of 98% with on-lay patch grafting without endarterectomy.[740]

The patency rate of on-lay patch grafting with endarterectomy varies according to the graft used, the endarter-

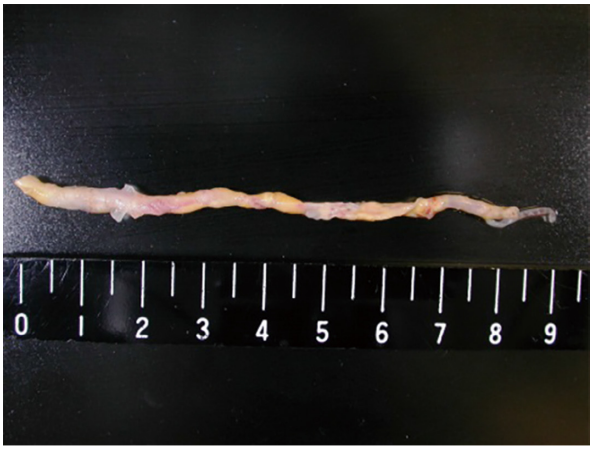


Figure 5. Intima removed by coronary endarterectomy.

Table 39. Recommendation and Evidence for Proximal Graft-to-Aorta Anastomosis

	COR	LOE
Aortic no-touch OPCAB for stroke reduction (more effective than side-clamp OPCAB)	I	B
Epiaortic ultrasonography for aortic wall assessment, evaluation of the feasibility and site of proximal graft-to-aorta anastomosis, and selection of clamp and cannulation sites	IIa	B
Use of assist device for graft-to-aorta anastomosis (alternative to side clamp) in the presence of moderate or severe aortic arteriosclerosis	IIa	B
Use of non-ITA graft as cuff (similar to pedicled graft) when free ITA graft is used	IIa	B
Proximal RA graft-to-aorta anastomosis (patency is similar to that of Y/I graft using ITA graft as inflow)	IIa	B

COR, class of recommendation; ITA, internal throarcic artery; LOE, level of evidence; OPCAB, off-pump coronary artery bypass; RA, radial artery.

ectomy method (closed or open), and the graft location among others. A study comparing the outcomes of on-lay patch grafting with closed or open endarterectomy reported a long-term patency rate of 89% for open endarterectomy and 81% for closed endarterectomy, revealing a statistically higher patency rate with the open method.[745] Schwann et al investigated by angiography the effect of the graft used on long-term patency and noted a higher patency for arterial grafts (ITA and RA) than for venous grafts.[746] The difference is probably for the same reason as the higher patency recorded for arterial grafts than for venous grafts in CABG in general. There is a report noting that the location of the endarterectomized artery has little effect on patency,[747] but there is no agreement on this point. Erdil et al performed on-lay patch grafting with closed endarterectomy in the RCA and reported a 100% long-term patency rate.[748] Nishigawa et al achieved ≥90% patency with the ITA anastomosed to the LAD with open endarterectomy.[749]

6. Proximal Graft-to-Aorta Anastomosis (Table 39)

The following points are to be considered in proximal graft-to-aorta anastomosis: (1) risk control of stroke resulting from the release of arteriosclerotic debris or gases caused by aortic manipulation, (2) suitability of the chosen graft (with a favorable long-term patency record) for proximal aortic anastomosis and technical aspects of anastomosis, and (3) long-term patency of the graft used in AC anastomosis.

6.1 Prevention of Related to Aortic Manipulation

6.1.1 Evaluation of Aortic Wall Thickness

Routine epiaortic ultrasonography is recommended for evaluation of aortic wall thickness. It is useful for deciding the suitability of proximal aortic anastomosis, site of anastomosis, clamp strategy, and cannulation site.[750–752]

6.1.2 ONCAB

The single-clamp technique for ONCAB completes the entire procedure including proximal aortic anastomosis with a single cross-clamp. In theory, this should reduce the risk of cerebral infarction compared with the double-clamp technique where side-clamping is applied after removal of the cross-clamp. However, there is no conclusive evidence on whether the single-clamp technique can actually reduce the occurrence of cerebral infarction.[753]

6.1.3 OPCAB

Aortic no-touch OPCAB lowers cerebral infarction risk compared with OPCAB with the side-clamp technique.[754] When the aortic condition is good, however, the superiority of an anastomosis assist device (Heart String, Enclose II) to the side-clamp technique has not been established (Class IIb, Level B). When epiaortic ultrasonography reveals moderate or severe aortic arteriosclerosis, the anastomosis assist device may lower the cerebral infarction risk more than side-clamping.[752,754–757]

Therefore, proximal graft-to-aorta anastomosis in OPCAB may be chosen over the aortic no-touch technique, after assessment of the patient's cerebral infarction risk, when it is expected to help avoid competitive flow or increase the likelihood of complete revascularization.

6.2 Indications and Procedures

6.2.1 SVG

An SVG should be anastomosed to the aorta unless aortic arteriosclerosis is severe (Class I, Level C). End-to-side anastomosis should be performed after careful selection of the site of anastomosis and graft orientation to avoid twisting of the graft.

6.2.2 RA Graft

No difference has been noted in long-term patency between RA graft used as a Y or I composite graft, with the pedicled ITA graft being used in proximal anastomosis and direct RA graft-to-aortic anastomosis.[758] Therefore, proximal aortic anastomosis is a viable option. Just as with the SVG, end-to-side anastomosis should be chosen for the RA graft.

6.2.3 Free ITA Graft

When the free ITA graft is used, sequential anastomosis can revascularize more coronary arteries (Class IIb, Level B).[759,760] Direct anastomosis to the ascending aorta is technically difficult and there is a risk of anastomosis site stenosis, especially in Japanese who tend to have thin ITAs. The piggyback/V graft technique by which the free ITA graft is anastomosed to the proximal aorta immediately above the SV/RA graft anastomosed to the ascending aorta can achieve at least equal long-term patency to that with the pedicled graft.[759,760] When a pedicled graft does not reach the target vessel, sequential anastomosis is required, or if the distal anastomosis is not thick enough, the free ITA may be used as a Y graft or as an AC graft by the piggyback/V graft technique.

6.2.4 Other Grafts

The GEA may be used in AC anastomosis (Class IIb, Level C).[761]

6.3 Graft Types, Outcomes, and Long-Term Patency

RA grafts when used as the 2nd graft after ITA graft show better long-term patency than SVGs, with a lower incidence of cardiac events and repeat revascularization (Class IIa, Level B).[684,762,763] However, when used as the 3rd arterial graft together with BITA graft, RA grafts may or may not attain better long-term outcomes compared with SVGs (Class IIb, Level C).[764]

Compared with SVGs, a free ITA graft in AC anastomosis retains superior patency (Class IIa, Level B).[759,760,763]

Table 40. Recommendation and Evidence for Graft Selection, Design, and Configuration

	COR	LOE
In situ LITA graft is recommended for revascularization of LAD	I	B
OPCAB with aorta no-touch technique utilizing an in situ arterial graft or composite graft is recommended in patients with a severely calcified ascending aorta	I	B
2nd arterial graft (RA or RITA) should be considered in low-risk patients	IIa	B
2nd arterial graft to the LCA territory is reasonable	IIa	C
BITA grafting is reasonable in patients without risk factors of sternal wound infection	IIa	B
BITA grafting should be considered in patients <70 years old	IIa	B
3rd arterial graft may be reasonable in patients with no perioperative risk factors and a long life expectancy	IIb	C
A skeletonized right GEA graft may be considered in the right coronary or circumflex territory with severe stenosis (≥90%) and adequate run-off	IIb	C
Sequential bypass using arterial grafts may be considered for multiple targets with severe stenoses (≥90%) that are in suitable locations	IIb	C

BITA, bilateral internal thoracic artery; COR, class of recommendation; GEA, gastroepiploic artery; LAD, left anterior descending coronary artery; LCA, left coronary artery; LITA, left internal thoracic artery; LOE, level of evidence; OPCAB, off-pump coronary artery bypass; RA, radial aretry; RITA, right internal thoracic artery.

Directly (AC) anastomosed free RITA and RA grafts share similar long-term cardiac event-free rates and patency (Class IIb, Level B). When used as the 2nd arterial graft in other than AC anastomosis, RITA grafts may achieve more favorable long-term results but may increase early complications (Class IIb, Level B).[687,763,765–767]

7. Graft Selection, Design, and Configuration (Table 40)

7.1 Selection of Graft Materials

7.1.1 First Arterial Graft

Normally, ITA grafts are used to construct a bypass to the LAD. ITA grafts have superior long-term patency, a higher cardiac event-free rate, and better survival benefit than SVGs.[494] The in situ ITA is generally the 1st choice for an ITA–LAD bypass.

7.1.2 Second Arterial Grafts

Until the 1990s, SITA grafts were commonly anastomosed to the LAD, with SVGs being the standard choice for other target vessels, such as the diagonal branch, LCX, and RCA. The high frequency of sternal wound infections from using BITA, and other previously reported issues, has discouraged arterial graft use. However, the establishment of calcium antagonists as a deterrent of RA vasospasm, as well as the ITA/GEA skeletonization technique enabling better preservation and protection of sternal blood flow and increased graft caliber and length, have provided additional evidence supporting the benefits of surgical techniques using a 2nd arterial graft in addition to the 1st arterial graft (ITA–LAD).

a. Target Vessel

The RITA, RA, and GEA are the candidates for the 2nd arterial graft. Generally, 2nd arterial grafts are suggested for use primarily in the LCA territory.[295,575,637,768,769] A meta-analysis by Karangelis et al indicated that the LCX should be the primary target of a 2nd arterial graft.[771] The primary reason for this is the generally higher patency rate of an arterial graft in the LCA than in the RCA territory, which can have a significant effect on patient survival.[772] In the RAPCO study that compared RA and SVGs in the construction of a bypass to the largest non-LAD vessel, grafts were used in the LCX in 70% of the cases.[676] Although the LCX should be considered first as the target of the 2nd arterial graft, the RCA may be the preferred vessel in appropriately selected patients who have an RCA, which is the most important vessel after the LAD.

b. Graft Material Comparisons

The results of RCTs comparing RA and SVGs are summarized in **Table 41**.[673–678,680–682,773,774] The RA graft was chosen because it is used in a manner similar to that of the SVG. How the SV and RA grafts were used in these studies, including the vessels to which they were anastomosed, is more important than whether or not the SV or RA was better overall when applying the findings to patients in the clinical setting. Many of the RCTs used the grafts for AC bypass and mostly (50–70%) in the LCX territory. The RA graft patency was generally more favorable than that of the SVG. However, although the outcomes with SVGs were unaffected by the degree of stenosis in the native coronary artery, an increased risk of physical or functional

Table 41. Comparison Between RA and SV Grafts

Reference	Author, year	Grafts	Study method	Sample size	Results	Follow-up (years), method	Graft usage, target	Inflow
673, 674	Desai/RAPS, 2004, Deb/RAPS, 2012	SV vs. RA	Randomized	561	RA had better patency	7.7, angiography	RCA or LCX with >70% stenosis and ≥1.5 mm diameter, randomized to RA or SV, LCX=50%	ACB 100%
675	Collins/RSVP, 2008	SV vs. RA	Randomized	142	RA had better patency	5, angiography	Randomized to different grafts used on the lateral target (primarily LCX)	ACB 100%
676	Hayward/ RAPCO, 2010 (Group 2)	SV vs. RA	Randomized	225	Similar patency rate, similar incidence of MACE	5.5	Randomized to different grafts chosen for the largest non-LAD target LCX:RCA:Dx= 70:25:5 for RA and 60:37:3 for SV	ACB
677	Goldman, 2011	SV vs. RA	Randomized	733	Similar patency	1, angiography	LAD:LCX:RCA was 14:59:27 for SV and 14:55:31 for RA	ACB=99% for SV and 92% for RA
773	Petrovic, 2015	SV vs. RA	Randomized	200	No difference in patency rate or event incidence	8	Target of RA: 74% to LCX, 9% to Dx, 17% to RCA	ACB
681	Cao, 2013	SV vs. RA	Meta-analysis	1,708	RA had better patency (short or medium term)	≥4		
774	Zhang, 2014	SV vs. RA	Meta-analysis		RA had better patency and less repeat revascularization	1–8		
682	Gaudino, 2018	SV vs. RA	Meta-analysis		RA had better patency rate for 5 years and less cardiac events	5.0		
680	Athanasiou, 2011	SV vs. RA	Meta-analysis		RA had better patency (for medium and long term)			
678	Benedetto, 2010	SV vs. RA	Meta-analysis		Similar patency			

ACB, aortocoronary bypass; Dx, diagonal branch; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MACE, major adverse cardiovascular events; RA, radial artery; RCA, right coronary artery; SV, saphenous vein.

Table 42. Comparison Between RITA and RA Graft

Reference	Author, year	Grafts	Study method	Sample size	Results	Follow-up (years)	Graft usage, target	Inflow
676	Hayward/ RAPCO, 2010 (Group 1)	RITA vs. RA	Randomized	394	Similar patency; RA had better clinical outcome at 6 years	5.5	Randomized to different grafts chosen for the largest non-LAD target LCX:RCA:LAD was 62:35:3 for RA and 69:25:6 for RITA	ACB
776	Caputo, 2003	RITA vs. RA	Retrospective	661	RA had higher event-free rate	1.79, 1.54	LAD:LCX:RCA was 16:31:53 for RITA and 4:58:38 for RA	RITA: 94% in situ and 6% in ACB RA: 78% in ACB and 22% as composite graft
685	Tranbaugh, 2014	RITA vs. RA	Retrospective	1,056	RA had less frequent MAE, a similar patency rate to RITA, and higher survival rate in aged individuals and COPD patients	9, 8.5	RA or RITA to LCX	ACB 100%
777	Ruttmann, 2011	RITA vs. RA	Retrospective	554	RITA had higher cardiac event-free rate and survival rate	4.8	RA: 94% in LCX BITA: 97% in LCA SITA+RA: 94% in LCA	In situ RITA: 58% in LCX, 18% as free RITA
778	Raja, 2015	Second ITA vs. RA	Retrospective	1,020	RITA had higher survival rate and less repeat revascularization	8	In situ ITA: 618 in LCX Y: 90 in LCX, 39 in RCA RA: 458 in LCX, 283 in RCA, 38 in Dx RA Y: 96 in LCX, 23 in RCA	RITA Y: 90 in LCX, 39 in RCA
779	Tranbaugh, 2017	RITA vs. RA vs. SV	Retrospective	13,324	RA and RITA had better results than SV in <70 years RA/RITA vs. SV not significantly different in ≥70-year-olds	8.8, 8.9, 9.1	RITA in LCX, RA in LCX	RITA: in situ or free
679	Hu, 2011	RITA vs. RA vs. SV	Meta-analysis		RA had less cardiac events than RITA, had similar survival rate, better patency, less wound infection			
780	Hwang, 2013	RITA vs. GEA	Retrospective	210	Patency rate and clinical outcomes similar after 5 years	Median of 6.7		100% Y composite graft, free GEA vs. free RITA
781	Benedetto, 2015	RITA vs. RA vs. GEA vs. SV	Meta-analysis		RITA and RA had better patency than SV; GEA had poorer patency than SV			

ACB, aortocoronary bypass; BITA, bilateral internal thoracic artery; COPD, chronic obstructive pulmonary disease; Dx, diagonal branch; GEA, gastroepiploic artery; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; LCA, left coronary artery; LCX, left circumflex coronary artery; MAE, major adverse events; RA, radial artery; RCA, right coronary artery; RITA, right internal thoracic artery; SITA, single internal thoracic artery; SV, saphenous vein; Y, Y graft.

Table 43. Comparisons Between BITA and SITA, and Between Secondary Grafts

Reference	Author, year	Grafts	Study method	Sample size	Results	Follow-up (years)	Graft usage, target	Inflow
687	Taggart/ART, 2016	BITA vs. SITA	Randomized	3,102	Similar 5-year event-free survival rate	10	BITA to LCA, ITA to other than RCA	BITA composite graft included
785	Iribarne, 2017	BITA vs. SITA	Retrospective	2,779	BITA had less repeat revascularization	13.2		
590	Lytle/ATS, 2004	BITA vs. SITA	Retrospective	2,304	BITA had higher long-term survival	16.2		
296	Lytle/JTCVS, 1999	BITA vs. SITA	Retrospective	10,124	BITA had higher long-term operation-free survival	10	61% to LAD+LCX, 23% to LAD+RCA	12% to 1 in situ and 1 free ITA, 87% to 2 in situ ITAs
786	Rubino, 2018	BITA vs. SITA (≥70 years)	Retrospective	1,608	BITA had frequent SWI in emergency cases	Short term		
787	DeSimone, 2018	BITA vs. SITA	Retrospective	2,594	BITA had higher survival rate	Long term		
788	Luthra, 2018	BITA+SV vs. BITA+arterial (ITA or RA)	Retrospective	334	No significant difference between SV and arterial grafts up until 8 years	7.0, 4.3	Mostly RA, 8.3% of RITA were to RCA	
688	Gaudino, 2017	3 arterial vs. 2 arterial grafts	Meta-analysis		3 arterial grafts had higher survival rate			
789	Hirose, 2002	BITA+RA vs. BITA+GEA	Retrospective	96 vs. 123	RA and GEA had similar patency rates and clinical outcomes	2.3	92% of GEA and 48% of RA to RCA	GEA; In situ RA; ACB, or composite graft
790	Di Mauro, 2009	BITA SV vs. BITA RA vs. BITA GEA	Retrospective	1,015	RCA stenosis <80%, SV superior to GEA	8.1	GEA and RA to RCA; BITA to LCA	In situ GEA
791	Pevni, 2005	BITA SV vs. BITA-Y vs. BITA GEA	Retrospective	619	RITA, SV, and GEA were similar in clinical outcomes	5.6	SV, GEA, and RITA to RCA; BITA to LCA	RITA, Y composite or in situ; SV, ACB
792	Grau, 2015	BITA SV vs. BITA RA	Retrospective	366	No significant difference overall; RA had higher survival rate at 10 years or later	10+	RA to RCA in 48%, SV to RCA in 54%, targeted mixed	
793	Gllineur, 2012	BITA SV vs. BITA GEA	Retrospective	297	GEA had higher survival rate	16.1	GEA to RCA; SVG to RCA	
649	Suzuki, 2011	BITA+SV vs. BITA+GEA skeletonized	Retrospective	170	GEA had higher survival rate and cardiac event-free rate	5.1	BITA to LCA In situ GEA or SVG to RCA±posterolateral branch	In situ GEA: SV=ACB
763	Schwann, 2016	RA-MAG vs. RITA-MAG vs. SAG	Multicenter, retrospective	1,653	SAG had poorer outcome than RITA-MAG or RA-MAG; SWI more frequent with RITA-MAG	0.25–15.75		RITA; 68% ACB, 32% in situ RA mostly used as ACB
794	Buxton, 2014	TAR vs. SITA-SV	Retrospective	768	TAR had better outcome than SITA-SV	10	RITA's target=22:34:12:36 for LAD:LCX:Dx:RCA; BITA in 36% of TAR	49% of RITA were free; RA was primarily as ACB including composite graft
795	Tatoulis, 2015	TAR vs. SITA-SV	Multicenter, retrospective	12,464	TAR had less early mortality and higher long-term survival rate than non-TAR	4.5	19% of BITA in RITA but mostly in LCX; RA in RCA	Y graft=18%
796	Glineur, 2016	In situ BITA vs. Y	Randomized	304	Y had lower incidence of cardiovascular/cerebrovascular events, MI+PCI, and MI+PCI+stroke	3.4±2.1	Y or in situ ITA in LCX (more anastomoses with ITA for Y); SV or GEA was used in other targets	No ACB
797	Gatti, 2018	In situ BITA vs. BITA-Y	Retrospective	80	Survival rate, stress test results, and patency were all similar	5.9	Y or in situ ITA in LCX	No ACB

ACB, aortocoronary bypass; BITA, bilateral internal thoracic artery; Dx, diagonal branch; GEA, gastroepiploic artery; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; LCA, left coronary artery; LCX, left circumflex coronary artery; MAG, multiple arterial grafts; MI, myocardial infarction; PCI, percutaneous coronary intervention; RA, radial artery; RCA, right coronary artery; RITA, right internal thoracic artery; SAG, single arterial graft; SITA, single internal thoracic artery; SV, saphenous vein; SVG, saphenous vein graft; SWI, sternal wound infection; TAR, total arterial revascularization; Y, Y graft.

(i.e., string sign) occlusion was observed for RA grafts when the degree of stenosis was <90%.[673] Additionally, the SV and RA are both prone to stenosis in the middle of the graft and at the site of anastomosis to the aorta.[673]

The results of RCTs comparing the RITA and RA as the 2nd arterial graft are presented in **Table 42**.[676,679,685,776–781] Both grafts were primarily used in the LCA territory, whereas, in some studies, RITA was occasionally used in the RCA. Superiority in graft patency of RITA or RA has not been conclusive. Use of the RITA has a risk of sternal wound infection. Regarding clinical outcome endpoints, such as the cardiac event-free rate and survival rate, some studies reported better results for the RA, whereas others indicated the superiority of the RITA. Compared with the SV, the RITA is superior in patency and freedom from events. In general, however, the RA and the RITA are equally suitable as the 2nd arterial graft of choice.

c. BITA

The ITA has intrinsic resistance to arteriosclerosis and rarely develops vasospasm or thrombus. Additionally, it is generally more suitable for bypass grafting than are other arterial grafts such as the RA and GEA. The BITA graft has been thought to have superior long-term outcomes, but the ART study report in 2016 found that the 5-year postoperative all-cause mortality or cardiac event-free (death, myocardial infarction, cerebral infarction) rate was no better for the BITA than for the SITA[687,782] (**Table 43**). Possible explanations for these results of the ART study are the conversion from BITA to SITA after randomization, which occurred in 14% of patients, and the inclusion of 22% of patients who received MAG (e.g., RA) in the SITA group. Moreover, the results suggested that the experience level of both the operators and institutions significantly affected the outcomes of CABG. Additionally, BITA grafts harvested and used by experienced operators are generally superior to SITA grafts.

The finding of an association between the harvesting technique for BITA and sternal wound infection led to a subgroup analysis in the ART study, which found that the risk of sternal wound infection with the skeletonized BITA was similar to that with a non-skeletonized SITA, but the risk with the non-skeletonized BITA was 1.8-fold higher than that of the skeletonized BITA.[615] Additionally, insulin therapy in DM patients, female sex, and high BMI were found to be independent risk factors of sternal wound infection.[615] Even when only the skeletonized SITA was used (to avoid the risk), sternal wound infection was not significantly decreased relative to that with the non-skeletonized SITA.[615] The mortality rate after a sternal wound infection has decreased to <20%,[783,784] thanks to the greater use of vacuum-assisted closure and infection control teams. Whether or not the BITA is beneficial should be decided while considering the patient's age and comorbidities.

d. Comparisons of Grafting Strategies

A substantial number of studies have compared SITA+SV against MAG (**Table 43**).[296,590,649,687,688,763,785–797] All such studies reported that MAG achieved better outcomes. A multicenter study conducted by Schwann et al revealed little difference between the MAG group using RITA graft, and the MAG group using the RA, but showed that both groups achieved better outcomes than those of the SITA group.[763] The total arterial revascularization (TAR) group had better outcomes than those of the SITA+SV group.[794]

Improvements in PCI outcomes over the years also encourage the use of arterial grafts in CABG. CABG with SITA+SV has few long-term benefits over PCI with DES.[798] The use of MAG is becoming the norm for CABG. The patient's life expectancy can still be a determinant of whether arterial grafts should be used. A report, however, found that multiple ITA/RA grafts can have short-term and long-term benefits even in patients aged ≥80 years.[799]

GEA can also potentially be used as a 2nd arterial graft, but is commonly regarded as a 3rd arterial graft choice because it is primarily used in the RCA.

7.1.3 Third Arterial Grafts

A limited number of reports have indicated that the use of a 3rd arterial graft can improve treatment outcomes. The effects of different grafts used in the RCA on the outcomes of CABG involving grafting of a BITA to the LCA have been investigated. BITA combined with a 3rd arterial graft has a beneficial effect on outcomes, especially long term (about 10 years).[649,688,790–793] Luthra et al reported that the outcomes of CABG with a 3rd arterial (e.g., RA) graft were similar to those with SVG for ≤8 years of follow-up.[788] Hirose et al noted no difference between the GEA and RA used as a 3rd graft.[789] Because some studies with a follow-up of >10 years have shown a statistically significant benefit, a 3rd arterial graft appears to be beneficial in some patient subgroups or selected patients.

The GEA is a preferred 3rd arterial graft. Hwang et al reported that the GEA achieved patency and outcomes similar to those of the free RITA, when used in the same manner, and concluded that the GEA clearly had great potential as a bypass graft.[780] In situ use of the GEA provides an independent inflow and imparts a significant advantage by eliminating the need for aortic manipulation. As an in situ graft, however, the intraluminal pressure of the GEA graft is approximately 10% lower than that of an ITA graft and 20% lower than that of the aorta, because of its anatomy.[800] In particular, for use in a coronary artery with moderate stenosis, the low pressure in the GEA can affect graft flow and patency. For this reason, careful selection of the target coronary artery is required when using the GEA. Based on the results of an RCT that compared the SV and GEA, Glineur et al stated that the GEA had a significantly lower functional patency rate than that of the SV when the degree of stenosis of the native coronary artery is ≤80%.[801] Suma et al stated that the GEA is indicated for ≥90% of stenoses.[633] Other researchers have proposed ≥80% stenosis as the threshold for GEA use.[801,802] Some surgeons consider the GEA to be the most suitable graft for stenosis in the proximal RCA (#1, #2, or #3) with a sizable territory.[803] The GEA also has been reported as unsuitable for a stenosis with a minimal luminal diameter ≥1.1 mm.[804] The criteria for the use of GEA have not been fully established.

The GEA is prone to functional occlusion, such as when poor graft flow is caused by moderate stenosis. The expected patency and benefits specific to GEA should be assessed in consideration of certain factors, such as the expected outcome, degree of stenosis, and flow demand, to select the patients or targets meeting these specific criteria.

7.1.4 Venous Grafts

Venous grafts, which are typically used by anastomosing their proximal side to the ascending aorta, have high

intraluminal pressure and graft flow capacity. However, ascending aorta manipulation is a risk factor for cerebral infarction. Venous grafts also have worse endothelial function than arterial grafts and are more susceptible to relatively early occlusion resulting from thrombus or hyperplasia and to long-term occlusion due to atherosclerosis of the venous wall. Venous grafts generally have a lower patency rate than that of arterial grafts. The use of an SVG is sometimes considered to be a risk factor itself.[805]

Nevertheless, unlike arterial grafts, the patency of venous grafts is less prone to the same degree of stenosis in the native coronary arteries, which makes venous grafts most suitable for use in the RCA with moderate stenosis, for which arterial grafts are not suitable because of the high risk of competitive flow.[804,806] Venous grafts are also preferred when the ITA is unlikely to provide sufficient bypass flow or when myocardial flow demand or vascular resistance is increased (e.g., in the acute phase of myocardial infarction).

7.2 Graft Configurations

The ART study, with a 5-year follow-up, found no notable differences between BITA and SITA. Other than the lower incidence of graft occlusion and the resulting lower frequency of myocardial infarction than with venous grafts, their report noted that potential bias might occur because of the diversity in how arterial grafts are used and configured, in part because of the lack of sufficiently experienced operators.[687] A study of graft flow also noted that graft configuration affected coronary circulation and may increase the risk of occlusion.[807] Graft configuration and design could affect both patency and treatment outcome.

7.2.1 Sequential Grafting

Anastomosis to multiple vessels may be required within the coronary territory because of diffuse coronary artery narrowing associated with DM and CKD or, especially in Japan, with repeated catheterization. Compared with an arrested heart, OPCAB better preserves the shape and size of the left ventricle and allows easy adjustment of the anastomosis angle and graft position. Because of the limited availability of usable arterial grafts and the risk of complications with harvesting, maximizing the potential of an arterial graft is required. Dion et al reported that patients treated by sequential anastomosis with the ITA maintained a favorable patency rate and had a low repeat revascularization rate during a mean follow-up of approximately 10 years.[808] Sequential grafting allows multiple anastomoses on 1 graft and is an essential technique in today's coronary artery surgery. However, it is technically demanding and associated with types of graft failure that are specific to this technique, and it may occur even when the anastomoses are constructed properly.

To achieve patency over the entire graft, sufficient antegrade flow must be obtained to the target artery anastomosed at the distal end of the graft. The site and angle of each anastomosis are adjusted to minimize the graft route. Sequential anastomosis in a diamond fashion can be a useful option.[573] With sequential anastomosis using an in situ ITA or one as inflow, the probability of attaining antegrade flow decreases when there is moderate stenosis in the target coronary artery anastomosed to the distal end of the graft. For this reason, a coronary artery with ≥90% stenosis should be selected for anastomosis with the distal end of a graft.[657,809] Conversely, a bypass graft anastomosed with the ascending aorta as inflow has a large flow capacity and high intraluminal pressure. Because venous grafts are largely unaffected by the degree of stenosis in the target artery, they are a suitable candidate when the target vessel has only moderate stenosis.

7.2.2 Composite Graft (In Situ Arterial Graft+Free Graft)

Aortic manipulation should be avoided in patients with severe calcification in the ascending aorta. If multivessel bypass grafting is feasible and safe, composite grafting should be a viable option for both complete revascularization and avoidance of cerebral complications. As in sequential anastomosis, attaining antegrade flow to multiple coronary arteries with a single graft requires careful patient and target vessel selection.

In particular, for composite grafts having a Y (or T) branch, the degree of stenosis in each of the anastomosed vessels has complex effects. To attain antegrade flow to both ends of the composite graft, each end must be anastomosed to a vessel with severe stenosis. In particular, interruption of the ITA–LAD bypass flow and patency must be avoided.[810]

Not many RCTs have compared different graft configurations. Glineur et al compared BITAs used as two in situ grafts to LAD and LCX with an in-situ LITA to LAD and a free RITA to LCA as a Y composite graft. The composite graft made sequential anastomosis easier, was usable for creating bypasses to more vessels with the ITA, and helped reduce cardiac events.[796] Based on their study comparing the outcomes of CABG with BITA, Magruder et al reported that graft configuration did not affect outcomes.[607] Their study assumed that operators selected the "optimal" graft configuration for individual patients, but the report did not describe how this optimization was performed.

For decades, optimal selection of grafts has been discussed. How the optimal graft configuration should be determined in individual patients is currently a matter of debate.

8. ONCAB and OPCAB (Table 44)

8.1 Outcomes in RCTs

A large number of RCTs have compared OPCAB vs. ONCAB. The ROOBY[811] was the first large-scale multicenter study of such RCTs. The incidence of the composite endpoint (mortality, myocardial infarction, and repeat revascularization) was similar at 30 days but higher for OPCAB after 1 year. More OPCAB patients had fewer grafts performed than planned. The graft patency rate after 1 year was significantly lower in the OPCAB group. The 5-year mortality rate was also significantly lower for

Table 44. Recommendation and Evidence for OPCAB

	COR	LOE
Experienced operator at an experienced institution	I	B
On high-risk patients	I	B
Use of aortic no-touch technique	I	B

COR, class of recommendation; LOE, level of evidence; OPCAB, off-pump coronary artery bypass.

OPCAB.[812] Criticism against the study included the inclusion of operators with limited experience in OPCAB and the enrollment of relatively young male patients. The CORONARY study[813] selected only operators with ample experience in OPCAB and reported that the incidence of the primary endpoint (composite of mortality, myocardial infarction, and cerebral infarction) was no different between OPCAB and ONCAB after 30 days, 1 year, and 5 years. More patients underwent repeat revascularization within 30 days in the OPCAB group, but no difference was observed after 5 years.[814] In the GOPCABE study, OPCAB was performed by experienced operators in patients aged ≥75 years. Little difference was seen in the composite endpoint of mortality, cerebral infarction, and myocardial infarction between OPCAB and ONCAB after 30 days or 12 months.[815] The SMART study[816] was an RCT in which all OPCAB procedures were performed by a single experienced operator. The study found no difference between OPCAB and ONCAB for survival and graft patency rates 1 year after surgery. The graft patency rate was also similar over a mean follow-up of 7.5 years. A higher survival rate was seen in the OPCAB group between 3 and 5 years later, with the difference narrowing slightly from 5 to 7 years.[817]

The JOCRI study[818] was a Japanese RCT in which only experienced operators participated. Only preliminary outcomes have been analyzed. Operative mortality and postoperative complications were no different between OPCAB and ONCAB. Graft patency rates were also similar.

The results of these prospective studies indicate that the outcomes of OPCAB performed by operators with ample experience are likely to be similar to those for ONCAB for up to nearly 5 years.

8.2 Volume-Outcome Relationship in OPCAB

Benedetto et al[819] searched through the Nationwide Inpatient Sample database to compare the effect of the annual number of patients operated on per operator or institution on outcomes for OPCAB and ONCAB. Among patients who had ≥2 vessels treated by CABG, OPCAB had a higher operative mortality rate than ONCAB when performed at an institution with <29 treated patients per year or by operators who performed the surgery on <19 patients per year. However, the operative mortality rate was lower for OPCAB performed at an institution with ≥164 treated patients per year or by operators who performed the surgery on ≥64 patients per year.

8.3 Advantages of OPCAB Over ONCAB

8.3.1 Outcomes in High-Risk Patients

Puskas et al[820] reported that OPCAB had a mortality benefit in patients with an STS predicted risk of mortality ≥2.5%, and that this mortality benefit increased as the predicted risk of mortality increased. A similar pattern was shown in a large-scale registry based on the STS database.[821] A meta-analysis in a recent RCT[822] indicated the incidence of operative death, myocardial infarction, and cerebral infarction with OPCAB decreased more markedly in patients with a less favorable risk profile.

8.3.2 Benefits of Aortic No-Touch Technique

A meta-analysis comparing the outcomes of OPCAB and ONCAB by the technique used for proximal aortic anastomosis[660] revealed that aortic no-touch OPCAB most effectively decreased cerebral infarctions, all-cause mortality, renal failure, bleeding, AF, and ICU stay. A study using the JCVSD[757] compared OPCAB using an anastomosis assist device with side-clamp OPCAB. Although early outcomes were similar, temporary neurological abnormalities were more frequent with side-clamp OPCAB.

8.3.3 Effects on Renal Function

A propensity-matched analysis using the STS database revealed a decrease in the incidence of in-hospital death and the hemodialysis rate after OPCAB among patients with baseline renal impairment.[823] The decrease was more marked in patients with more severe baseline renal impairment. An analysis using the JCVSD indicated progression to hemodialysis was significantly less frequent among patients with an eGFR <30 mL/min/1.73 m^2 and who underwent OPCAB.[824]

8.4 Cerebral Infarction

A meta-analysis of RCT data indicated OPCAB lowers the incidence of cerebral infarction.[825]

9. Intraoperative Graft Evaluation

9.1 Intraoperative Fluorescence Imaging (IFI; Table 45)

9.1.1 Benefits of Semiquantitative Analysis

Indocyanine green (ICG) used with a near-infrared light source was developed by the Kodak Research Laboratories and has been used in diagnostic imaging since 1956. A large number of papers on surgeries performed using ICG in different clinical areas have been published over the years.[826] In the field of cardiovascular surgery, IFI with ICG was first reported in 2002.[827] Subsequently, Taggart et al, Reuthebuch et al, Takahashi et al, and Balacumaraswami et al have reported on graft validation using IFI.[828–831] In 2005, the FDA granted approval for coronary angiography using ICG. Before the clinical application of IFI with ICG, graft evaluation with transit-time flowmeter (TTFM) was the only quantitative technique. IFI enabled real-time videorecording of blood flow in bypass grafts and the native coronary artery while the patient's heart was exposed (**Figure 6**).

Detecting technical errors in anastomosed grafts during CABG certainly helps improve the surgical outcome. IFI has the highest sensitivity among all the techniques in use for intraoperative graft validation, making it suitable for use in CABG.[826] IFI does not require catheterization of any graft or iodine contrast medium and therefore has no adverse effect on renal function or cause radiological exposure, making it a minimally-invasive technique for intraoperative graft assessment.[832–834]

Although OPCAB is chosen in ≥60% of CABG per-

Table 45. Recommendation and Evidence for IFI

	COR	LOE
Intraoperative graft validation during CABG using IFI with indocyanine green	IIa	B

CABG, coronary artery bypass grafting; COR, class of recommendation; IFI, intraoperative fluorescence imaging; LOE, level of evidence.

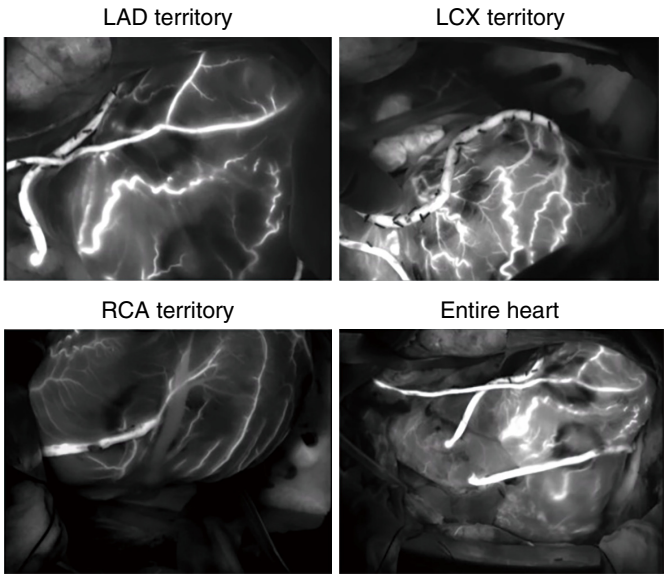


Figure 6. Intraoperative fluorescence imaging with indocyanine green visualizes grafts to the LAD, RCA, and LCX territories and in the heart as a whole. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

formed in Japan,[835] it is technically demanding and may have the disadvantage of decreasing the graft patency rate. Combining a visual graft evaluation technique with TTFM helps improve the outcome of the surgery. The 2011 American College of Cardiology Foundation (ACCF)/AHA Guideline[836] states that IFI enables "semiquantitative" graft validation method during CABG by visualizing the bypass grafts using ICG fluorescence.

9.1.2 Clinical Outcomes

In 2009, the Centers for Medicare and Medicaid Services in the USA reported that CABG patients who underwent intraoperative fluorescence vascular angiography (IFVA) with ICG had a shorter average hospital stay, by approximately 1 day, and a lower average medical cost than those who did not undergo IFVA with ICG. Concerning the IFI method using ICG, noncoronary IFVA had been covered by insurance as ICD Code 17.71, and coronary IFVA had been covered under ICD Code 88.59 in the past.[837] Currently, the code for coronary IFVA is updated to ICD 10 Code 4A12XSH (Monitoring of Cardiac Vascular Perfusion using Indocyanine Green Dye, External Approach).

The National Institute for Health and Care Excellence in the UK refers to IFVA as a safe and effective method for the evaluation of CABG patency under its guideline (Interventional Procedure Guidance 98).[838]

Balacumaraswami et al[839] reported insufficient blood flow in 8 (3%) of 266 grafts by IFI during CABG and re-anastomosed those grafts. TTFM suggested possibly insufficient blood flow in 10 grafts in 10 patients, but none of the grafts were re-anastomosed because IFI detected sufficient flow. The authors concluded that IFI is superior to TTFM in terms of accuracy of graft patency evaluation. Waseda et al[840] compared IFI, TTFM, and postoperative coronary angiography in 137 patients who underwent CABG (507 grafts were used). IFI indicated poorly constructed anastomoses in 6 patients, but TTFM failed to identify any of them. On the other hand, TTFM suggested re-anastomosis of 21 grafts that IFI revealed as no issue. The authors concluded IFI is useful for intraoperative assessment of anastomosed graft patency and helps avoid early graft failure associated with technical errors. Desai et al performed both IFI and TTFM and compared the findings with postoperative coronary angiography in an RCT in 106 patients.[841] IFI was shown to have superior sensitivity compared with TTFM (P=0.023) and was more accurate in detecting graft failure.

9.2 TTFM

Numerous articles have attested to the importance of graft assessment during CABG for improving and maintaining the quality of CABG. Intraoperative graft evaluation techniques include those for morphology assessment, such as angiography, IFI using ICG, and ultrasonography as well as quantitative techniques that measure graft flow. Coronary angiography is an invasive and time-consuming procedure and not suitable for intraoperative evaluation. IFI is a relatively easy technique and useful, but is yet to be widely accepted.[826] Ultrasound imaging only requires a probe for the heart surface, but it is suitable only for evaluation of a narrow area, and accurate evaluation is sometimes difficult with the 2-dimensional imaging.[842] Compared with these, TTFM is easy and reproducible, and thus most commonly used for intraoperative graft assessment.[843] With TTFM, mean graft flow, pulsatility index (PI), and diastolic filling index (DFI) are the common measures. These 3 measures are used in intraoperative graft evaluation (to detect anastomotic errors and whether revision is necessary).

9.2.1 Mean Graft Flow

Unlike in other organs, the majority of blood flow in the coronary artery occurs during diastole. Graft flow is recognizable during diastole when adequate flow is obtained. When the absolute graft flow or graft flow during diastole is low, competitive flow, vasospasm or graft failure such as dissection or anastomotic failure is suspected.

Beating CABG allows graft evaluation with TTFM after each anastomosis. For example, placing a suture for

Table 46. Measurement of In-Graft Flow and PI Using Transit-Time Flowmeter

	Observation	Possible scenario
Mean graft flow (Qm)	≥20 mL/min	Normal in general, but a high PI may be an indication of abnormalities at the site of anastomosis
	<20 mL/min	Some abnormality should be suspected for the graft, anastomosis or target coronary artery
Blockage at proximal side of target coronary artery	Qm unchanged + normal diastolic pressure	Competitive flow, stenosis at the proximal side of the anastomosis
	Qm decreased + diastolic pressure decreased	Abnormality in distal coronary artery, stenosis at the distal side of the anastomosis, or small perfusion territory in the distal side of the anastomosis
	Qm increased	Competitive flow, no abnormality in the distal side of the anastomosis
Blockage at distal side of target coronary artery	Qm decreased	No abnormality in the distal side of anastomosis; competitive flow; stenosis in the proximal side of the anastomosis
PI	<5	Low resistance to graft flow
	≥5	Stenosis at the anastomotic side; residual stenosis in the distal side of the anastomosis

PI, pulsatility index.

blood blockage around the vessel at the proximal and distal sides of each anastomotic site allows measurement of (1) uninterrupted graft flow, (2) graft flow when the proximal side is blocked, and (3) graft flow when the distal side is blocked after the anastomosis is constructed. This technique helps detect stenosis or occlusion in the proximal and/or distal side of an anastomosis, as well as competition between the coronary artery flow and graft flow (**Table 46**).

With ONCAB, accurate graft flow measurement is possible only after construction of all anastomoses, recovery of cardiac contractility and systolic blood presure.

9.2.2 PI and DFI

The PI is calculated by "(maximum flow−minimum flow)/mean flow". PI represents the flow pattern and resistance: a high values means a high resistance against graft flow and suggests residual stenosis in the target artery, graft spasm/stenosis, or other problems at the distal anastomosis.

The DFI is calculated as percentage by "100×diastolic flow/(diastolic flow+systolic flow)". Systolic flow and diastolic flow are calculated using the interval from the R wave peak to the T wave peak on ECG as the systolic phase. DFI represents the ratio of diastolic flow to graft flow. A high DFI indicates a high ratio of diastolic flow and that the graft flow matches the flow pattern of the coronary artery.

9.2.3 Criteria for Revision

For evaluation of graft failure using TTFM, the following cutoff points for acute graft failure have been proposed based on comparisons with postoperative angiograms: 15 mL/min or 20 mL/min for mean graft flow, 11.5 mL/min for an arterial graft, 15 mL/min for the LCA, and 20 mL/min for the RCA.[843–846] For PI and DFI, respectively >5 and >50% have been frequently reported as reference points. Normally, a graft flow rate of ≥20 mL/min and a PI <5 are recommended as cutoff points.

When a TTFM measurement deviates from the cutoff points, whether the deviation was caused by the graft, anastomosis or the lesion in the target coronary artery should be assessed to decide whether revision is required. Combining quantitative analysis by TTFM with a modality that allows morphological assessment enables accurate graft evaluation and helps achieve consistent quality of care for CABG.[847]

10. CABG Outcome Registry

Case registries of coronary artery revascularization have been around for many years, though mostly in Europe and the USA.

Because the development of a nationwide database in Japan did not come about until recently, individual institutions have created their own case registries and evaluated risk prediction models developed outside Japan using their own data.[848] The JATS has collected case information (including operative mortality) from >90% of relevant institutions in Japan through their questionnaire survey and have reportedly collected data annually[458] since 1986. The annually reported data are critically important as Japanese statistics of cardiovascular surgeries. However, because no preoperative information is included, only the crude mortality rate, not the risk-adjusted, can be drawn from the data. The number of CABG cases peaked around 2003 and has been decreasing in recent years in Japan.

In 2002 the Japanese Association for Coronary Artery Surgery started an annual national questionnaire survey intended to collect more complete data specific to coronary artery surgery. They send questionnaires to about 300 institutions where coronary artery surgery is performed, with a response rate of about 60%. The data collected in the survey are published on their website.[849] Although the survey does not register all cases, it provides valuable information about coronary artery surgery performed in Japan. According to the survey in 2017, OPCAB accounted for 64% of CABGs performed at the responding institutions. The mortality rate was 1.52% for isolated CABG, 0.81% for initial elective CABG, and 0.61% for initial elective OPCAB without conversion to cardiopulmonary bypass.[849]

Long after the development of similar databases in Europe/USA, the development of a nationwide database of cardiovascular surgeries with baseline risk information gained momentum in Japan. This movement was fueled partly by certain medical malpractice lawsuits in the cardiovascular field that captured media attention. The JCVSD was established in 2000 and started registration of CABG cases. Only 5 institutions participated at the launch of the database, but others gradually followed suit.

Japanese and American nationwide databases publish annual reports. According to the STS report in 2018,

156,931 CABG cases were registered in 2016. The operative mortality rate (30-day mortality+in-hospital mortality) was 2.2%, and OPCAB accounted for about 13% of all CABG cases.[850] The JCVSD published a report for the years 2013 and 2014 in 2018. The total number of CABG performed in the 2 years was about 32,000. The operative mortality rate was 3.0%, and the percentage of OPCAB in all CABG cases was 55%.[851,852] The operative mortality rate for elective CABG and elective OPCAB was, respectively, 2.0% and 1.1%. A questionnaire survey conducted by the Japanese Association for Coronary Artery Surgery boasted better numbers, but the JCVSD report is probably more accurate because of the higher coverage of cases.

A CABG registry is an essential tool that allows an operator to ojectively look at the results of invasive surgeries he/she has performed. It is also important for cardiologists. Case registries are aimed at providing quality information to all physicians in the field.

VII. PCI Techniques

1. Strategies to Improve Prognosis

The history of PCI started with POBA performed by Gruentzig et al. on September 16, 1977.[853] In 1986, Sigwart et al[854] and Serruys et al[855] introduced the BMS, which was shown to be effective particularly for acute coronary occlusion after balloon dilatation and quickly gained acceptance.[854–856] ISR was, however, reported in approximately 30% of BMS cases and came to be known as the Achilles' heel of PCI.[857,858] Development of the DES was intended to solve the problem of ISR. The first DES was used by Sousa et al. in 1999.[859] In this manner, the major developments in PCI-related techniques occurred at intervals of about 10 years.

The 1st-generation DES had mixed results due to VLST, but 2nd-generation DES are largely free from VLST and have become the first choice in PCI regardless of the characteristics of CAD. The scenarios where a BMS has the advantage over a DES are now very limited. The ESC/EACTS guidelines of 2018 recommend new-generation DES as the first choice for all PCI.[64]

Development of new stents has led to improved clinical outcomes of PCI over the years. In multivessel or other complex disease (e.g., patients with DM), however, PCI is still unable to improve survival as much as CABG. Studies to further improve the outcomes of PCI are ongoing. One of the fruits of such studies is the 5 general recommendations for maximizing the survival benefit of PCI (**Table 47**). These constitute today's core PCI strategies.

One of these strategies is PCI guided by the severity of functional stenosis (ischemia). Traditionally, PCI was guided by visual assessment of stenosis (or guided by angiography). This changed when the benefit of PCI guided by FFR (or guided by ischemia) was reported in a series of studies, including DEFER, FAME, and FAME 2.[34,36,134] The DEFER study reported the outcomes of PCI with 15-year follow-up and demonstrated the safety of deferring PCI based on ischemia assessment in patients on OMT.[35] The COURAGE and BARI 2D studies compared angiography-guided PCI with OMT and failed to demonstrate the superiority of PCI in reducing cardiovascular events.[88,89] However, the 5-year follow-up of the FAME 2 study with a comparison of ischemia-guided PCI and medical therapy revealed PCI decreased myocardial infarction compared with medical therapy.[860]

Stent placement guided by IVUS is another key PCI strategy. Evidence on IVUS was previously limited to PCI in complex disease such as LMCA lesions. An all-comers RCT comparing angiography-guided and IVUS-guided stent placement indicated IVUS-guided stent placement could improve the outcomes of PCI further in the era of DES.[861]

Complete revascularization is also one of the key PCI strategies. The SYNTAX study reported that long-term death and myocardial infarction occurred more frequently after PCI than CABG and attributed the differences partly to the lower percentage of complete revascularization achieved with PCI compared with CABG.[862] CTO and microvascular disease are the main causes of incomplete revascularization, although the outcomes of PCI in CTO lesions have improved significantly in recent years.[863] The DCB was also shown to be as effective as DES for the treatment of microvessel disease in the BASKET-SMALL study.[864] Today, PCI should therefore aim for complete revascularization when it is feasible and safe, considering the size of ischemic area.

Combining the above 3 strategies is required to maximize the survival benefit of PCI. The SYNTAX II study assessed the suitability of PCI using iFR, placed stents guided by IVUS, and reported recanalization of CTO at a high success rate. The study became a textbook example of the latest PCI strategies. The outcomes of PCI reported in the study also equaled those of CABG in the SYNTAX study.[865] The results of the SYNTAX II study at the same time indicated there is still room for improvement in PCI. The study reported that the number of lesions treated per patient was 2.6, compared with 4.0 in the SYNTAX study, and that the percentage of patients with 3-vessel disease was 37.2% vs. 83.3%. PCI guided by the current and most suitable techniques can increase its survival benefit and also make it a cost-effective treatment.

Table 47. Recommendation and Evidence for General Strategies in PCI

	COR	LOE
PCI guided by severity of functional stenosis (ischemia)	I	A
Imaging-guided stent placement	I	A
Complete revascularization guided by perfusion area and ischemia	I	A
Consideration of hemorrhagic complications and contrast-induced nephropathy in PCI	I	B
Optimal medical therapy and lifestyle intervention	I	A

COR, class of recommendation; LOE, level of evidence; PCI, percutaneous coronary intervention.

Table 48. Recommendation and Evidence for Access Site for Percutaneous Coronary Intervention		
	COR	LOE
Use of radial artery as an access site	I	A

COR, class of recommendation; LOE, level of evidence.

Considering the risk of hemorrhagic complications and CIN is also an important PCI strategy. The combination of perioperative bleeding and CIN has been reported as a prognostic determinant. Meta-analyses revealed RA access is superior to femoral artery access for both the risk of bleeding complications and CIN.[866,867] Ingenuity may also be needed to adjust the contrast dose depending on the patient's renal function.

Combining OMT, tailored to the patient with the goal of managing classic risk factors such as diabetes, hypertension, dyslipidemia, obesity, and smoking, with lifestyle interventions such as smoking cessation, diet therapy, and acquisition of exercise habits is the last of the 5 core PCI strategies. Long-term prognosis after revascularization has been shown to vary between patients with and without OMT. In OMT, proactive risk management needs to be combined with antithrombotic therapy that balances ischemia and hemorrhagic complications.[868,869]

2. Access Site (Table 48)

Femoral artery access and RA access for angioplasty and PCI were compared in RCTs, among which the RIVAL and MATRIX studies are well known.[870,871]

The RIVAL study enrolled 7,201 patients and showed no difference in 30-day event rate (mortality, myocardial infarction, stroke, or major bleeding unrelated to CABG) between femoral artery access and RA access, but the RA approach significantly decreased access site complications (HR, 0.30; 95% CI, 0.13–0.71; P=0.006).

In the MATRIX study, 8,404 patients with ACS were enrolled. The 30-day net adverse clinical event (MACE or major bleeding) rate and the incidence of Bleeding Academic Research Consortium (BARC) 3 or 5 major bleeding were significantly lower in the radial artery access group (major bleeding, 1.6% vs. 2.3%; relative risk, 0.67; 95% CI, 0.49–0.92; P=0.013). RA access decreased all-cause mortality rate (1.6% vs. 2.2%; relative risk, 0.72; 95% CI, 0.53–0.99; P=0.045).

A meta-analysis of data from over 600,000 patients in observational studies and RCTs showed RA access reduced hemorrhagic complications by 78% and post-procedural blood transfusion by 80% compared with femoral artery access.[866] Also, the RA approach is linked to lower risk of renal impairment.[867,872]

Based on these and other related data, RA access is the commonly recommended route of access for PCI.

3. POBA

POBA was first performed in Zurich in 1977 and soon faced considerable criticism. It nevertheless gained popularity because of the less invasive nature of the procedure compared with other options.[853] PCI used to be called percutaneous transluminal coronary angioplasty (PTCA).

Initially, PTCA involved compression of the atheroma and disruption of the artery wall, but the efficacy of atheroma compression/removal was very limited. Artery wall dissection and recoil were unavoidable with the procedure involving balloon dilatation alone. PTCA in its early days was therefore troubled by frequent acute coronary occlusion and restenosis in the chronic phase. Debates ensued on the appropriate balloon size and dilatation technique, but little improvement in clinical outcome followed.[873,874]

4. BMS

To overcome the limitation of balloon dilatation, the coronary artery stent was introduced to support the lumen against recoil. The use of the first BMS, Wallstent™, was reported by Sigwart et al[854] and Serruys et al[855] among others.[856] The BMS was shown to be particularly effective for reducing acute coronary occlusion resulting from arterial dissection after balloon dilatation. In 1994, Serruys et al conducted the BENESTENT study, the world's first RCT of BMS (Palmaz–Schatz stent).[858] The study enrolled 516 patients with stable angina. In the balloon-alone group, chronic cardiac events and cerebrovascular disease were reported in 76 (30%) patients, compared with 52 patients (20%) in the stent group, showing a statistically significant difference (P=0.017). Also, the incidence of restenosis, assessed by quantitative coronary angiography, was 22% in the stent group, significantly lower than the 32% in the balloon-alone group (P<0.05).[858] The superiority of stent placement to the balloon-alone procedure was established by the BENESTENT study.[858]

The widely accepted minimum duration of DAPT after BMS placement in stable CAD is 1 month. BMS is a reasonable option in a patient who cannot continue antiplatelet therapy for longer than 1 month for any reason. However, BMS revealed no advantages over DES in patients who had discontinued DAPT early for any reason (e.g., for surgery) and also in RCTs in patients who were at increased risk of bleeding and received 1 month of DAPT.[454,875–878] The ESC/EACTS guidelines of 2018 recommend the use of new-generation DES instead of BMS in any patient undergoing myocardial revascularization.[139] The spread of new-generation DES has significantly limited the clinical scenarios where BMS is a viable option.

5. DES (Table 49)

The rate of restenosis after PCI decreased to about 20–30% after the development of the BMS, but ISR remained the vulnerability of PCI.[857,858] DES took the place of BMS by mostly overcoming restenosis.[859] Eluting a drug to inhibit neointimal formation dramatically decreased chronic restenosis and achieved a marked reduction in repeat revascularization.

5.1 1st-Generation DES

The world's first clinically used DES contained sirolimus, the immunosuppressive compound isolated from a fungus in Easter Island.[879] The first-in-human clinical trial of DES

reported no ISR in 6 months and only once in 1 out of 30 patients by 3 years later.[859] Serruys et al reported 0% restenosis after 6 months and a 1-year MACE rate of 5.8% in the multicenter RAVEL study in 238 patients.[880] The SIRIUS study in the USA used the SES. It was larger in scale than and almost contemporary to the RAVEL study. SIRIUS enrolled 1,058 patients with stable or unstable angina and demonstrated overwhelming superiority of the SES (P<0.001).[881] In Japan, the SES was launched in 2004.

After SES, paclitaxel drew attention for its immunosuppressant and cytostatic activities and as a drug to be incorporated into stents. In the first paclitaxel-eluting stent (PES), paclitaxel was conjugated to a biocompatible polymer and applied as a stent coating. PES was launched in 2007 in Japan.[882]

Adverse effects specific to DES, such as VLST, then came to light. According to a report from Rotterdam, the incidence of VLST was about 0.6% per year. In a 7-year follow-up of 5,078 Japanese patients who had SES placed, the incidence of VLST was 1.43%.[883,884] Delayed and incomplete re-endothelialization of the stent and inflammatory response to the polymer, among others, have been purported as possible causes of VLST, but the true mechanisms remain unclear.[885–887] There are a large number of patients who still have a first-generation DES (SES, PES) and although the reported incidence of VLST is low, it is an ongoing concern for these patients.

5.2 2nd- and 3rd-Generation DES

The 2nd- and later generation DES are made of drug-eluting durable polymers with greater biocompatibility for improved safety, combined with changes in materials and strut thickness. Medium- to long-term mortality rates and myocardial infarction rate are similar between newer durable-polymer DES and BMS. However, durable-polymer DES have a significantly lower incidence of subacute and LST and share a similar or lower incidence of VLST vs. BMS.[888,889] The EES, constructed with a highly biocompatible polymer, is a 2nd-generation DES that has been in use since 2010 in Japan.

Table 49. Recommendation and Evidence for DES

	COR	LOE
Use DES for all PCI	I	A

COR, class of recommendation; DES, drug eluting stent; LOE, level of evidence; PCI, percutaneous coronary intervention.

The 3rd-generation DES are made of biodegradable polymer and show similar characteristics to BMS after the end of drug release and polymer biodegradation. A number of thin-strut, biodegradable-polymer DES (Ultimaster™, Synergy™, Osiro™) have been released since 2015. Numerous clinical trials have compared biodegradable-polymer DES and durable-polymer DES,[890,891] but only the BIOFLOW V study has so far reported a lower incidence of 12-month target lesion failure for biodegradable-polymer DES vs. durable-polymer DES (P=0.0399).[892] The SORT OUT IV study did not find conclusive evidence.[893] Short-term DAPT (1 month in stable angina and 6 months in ACS) combined with PCI in the SENIOR study revealed a similar safety profile between biodegradable-polymer DES and BMS, and superior efficacy of biodegradable-polymer DES.[877]

Whether 2nd- and 3rd-generation DES truly have different class effects and in what scenarios (clinical background and presentation) such effects will be achieved are yet to be uncovered. A list of commonly used DES is presented in **Table 50**.

Restenosis in diffuse/multivessel/microvascular disease and CTO lesions as well as ISR reported frequently with older DES have been decreased with new-generation DES (the overall restenosis rate is now estimated to be <10%). Consequently, indications for PCI have expanded to lesions that used to be difficult to treat or were contraindicated with PCI, including LMCA lesions. Also, DES is taking over BMS as the first choice for use in PCI in ACS, in particular ST-segment elevation myocardial infarction (STEMI).[894]

Table 50. 2nd-Generation and Later DES Available in Japan (as of October 2018)

	Stent platform	Polymer coating	Drug	No. of links
Double polymer coating				
Promus Premier	Platinum chromium	PBMA, PVDF-HFP	Everolimus	2–4
Resolute	Cobalt alloy	PBMA, PHMA, PVP, PVA	Zotarolimus	1.5–2.5
Xience	Cobalt chromium	PBMA, PVDF-HFP	Everolimus	3
Biodegradable polymer coating				
Nobori	Stainless-steel	PDLLA	Biolimus A9	2
Orsiro	Cobalt chromium	PLLA	Sirolimus	3–4
Synergy	Platinum chromium	PLGA	Everolimus	2–4
Ultimaster	Cobalt chromium	PDLLA, PCL	Sirolimus	2
No polymer coating				
BioFreedom	Stainless-steel	–	Biolimus A9	2–3

DES, drug eluting stent; PBMA, poly n-butyl-methacrylate; PCL, poly caprolactone; PDLLA, poly d,l-lactide; PHMA, poly hexyl methacrylate; PLGA, polylactic acid-glycolic acid; PLLA, poly-L-lactic acid; PVA, polyvinyl alcohol; PVDF-HFP, polyvinylidene fluoride hexafluoropropylene; PVP, polyvinyl pyrrolidone.

Table 51. Recommendation and Evidence for Use of the Atherectomy Catheter		
	COR	LOE
Use of Rotablator in calcified lesion	IIa	B
Use of DCA in bifurcation lesion	IIb	C

COR, class of recommendation; DCA, directional coronary atherectomy; LOE, level of evidence.

6. Special Balloons

6.1 DCB

DCB refers to balloons that are coated with highly liposoluble paclitaxel and designed to apply the drug to the vascular wall through balloon dilatation. Different DCBs have had mixed results, but mostly have been shown to be effective for reducing ISR. DCB is more effective than POBA against BMS restenosis and as effective as in-stent placement of new-generation DES, but it is considered to have greater angiographic late lumen loss than DES.[435,895] In treatment of restenosis after DES placement, DCB have had mixed results and no reports have shown the risk of late lumen loss is lower for DCB compared with new-generation DES. None of the previous studies reporting on the survival benefit of DCB has had adequate statistical power due to limitations such as follow-up period and sample size. However, network meta-analyses indicate that new-generation DES and DCB have similar efficacy in reducing repeat revascularization.[896,897] Evidence suggests DCB has benefit against small vessel disease. The use of DCB is also approved for <3 mm de novo CAD.

6.2 Cutting Balloon

Cutting balloon catheters are used to dilate stenotic segments that are difficult to dilate by conventional POBA. A cutting balloon catheter has 3 or 4 parallel blades in the longitudinal direction. Inflating the balloon pushes the blades against and makes cuts in the plaque, allowing dilatation of the segment with minimal pressure. Use of a cutting balloon enables dilatation of a stenotic segment without the risk of severe coronary artery dissection, but it can cause coronary artery perforation. In the case of coronary artery hematoma, a cutting balloon can cut the intima and create an entry from the false lumen to the true lumen.

The REDUCE III study was a Japanese study investigating the benefit of cutting balloon angioplasty before BMS placement.[898] The rate of restenosis in patients who had BMS placed after IVUS-guided cutting balloon angioplasty was 6.6% and significantly lower than the 17.9% for BMS placed after angiography-guided cutting balloon angioplasty, 19.8% for BMS placed after IVUS-guided balloon angioplasty, and 18.2% for BMS placed after angiography-guided balloon angioplasty. Therefore, IVUS-guided cutting balloon angioplasty has been suggested to be a useful pretreatment for stent placement.

6.3 Scoring Balloon

Scoring balloons (AngioSculpt® Balloon Catheter, Lacrosse NSE® Balloon Catheter) have scoring elements such as wire (rather than blades) on the balloon to reduce the risk of coronary artery perforation that may occur with cutting balloon. They can achieve good dilatation in segments where a normal balloon cannot (e.g., due to slipping).

6.4 Perfusion Balloon Catheter

Perfusion balloon catheters can dilate the narrowed segment for an extended period while maintaining coronary blood flow. They are used to achieve hemostasis in the event of coronary artery perforation. Withdrawing the guidewire to the perfusion marker can increase blood flow to the balloon tip.

7. Atherectomy Catheter (Table 51)

Various devices have been developed with the hope of overcoming the problem of restenosis. In the early 1990s, atherectomy and laser systems were successively released and collectively called "new devices" at the time. However, none of them effectively decreased restenosis compared with BMS and despite initially drawing attention, many of them were never in common use.

7.1 Rotablator and the Orbital Atherectomy Catheter

The Rotablator® (high-speed rotational percutaneous atherectomy system) was approved in 1997 in Japan. Initially, it was not expected to show efficacy in restenosis reduction.[899–902] PCI is still not entirely effective when severe calcification is present and the Rotablator has become a necessary tool for the treatment of heavily calcified segments, which are often found in dialysis patients.[903] The CVIT registry reported that the Rotablator was used in 3.2% of PCI performed in 2014 and 2015, and the incidence of major complications and cardiac tamponade in PCI using Rotablator was 1.3% and 0.6%, respectively.[904]

In 2017, the new Orbital Atherectomy System® for use in calcified segments was included in the Japanese National Health Insurance price list. The aim of the Orbital Atherectomy System is improving the success rate of PCI by sufficient dilation of heavily calcified segments. The ORBIT II and COAST studies reported that the system is useful for assisting dilatation of calcified lesions,[905] but evidence supporting its benefit is still insufficient. More data are needed with accumulation of user experience for overall assessment.

7.2 Directional Coronary Atherectomy (DCA)

The only DCA device was discontinued in 2008, and the previous version of our guideline did not include any information about DCA. In 2015, however, a Japanese manufacturer relaunched the device. It was initially unable to show benefit over BMS, but the OARS study[906] and ABACAS study[907] in which DCA was performed with IVUS guidance reported that the device lowered the restenosis rate more than BMS. Because DES were developed around the same time as the reports of these studies, however, DCA was not given the opportunity to be tested globally.

DCA is capable of curtailing carina shift and plaque shift

during treatment of bifurcation lesions. The multicenter PERFECT registry of DCA+SES in bifurcation lesions reported an overall TLR rate of 1% and 0 TLR in the subgroup of patients with bifurcation lesions in LMCA.[908] Synergistic effects of DCA with stent placement were therefore indicated.[909]

No data about DCA have been published since the relaunch. DCA may prove useful as a supportive device for DES or DCB in PCI in bifurcation lesions.

7.3 Excimer Laser Coronary Angioplasty (ELCA)

ELCA was first used in PCI in 1992 and is a relatively old technique. Because various complications, such as perforation and dissection, were frequently reported, ELCA failed to gain acceptance for many years. Subsequent technical advances improved the safety of the technique, but ELCA remained an experimental treatment used by a limited number of institutions until recently because its benefit remained in doubt. When its utility for withdrawal of pacemaker leads was reported, however, ELCA came into the spotlight. In 2012, ELCA was granted an indication for coronary artery intervention in Japan.

The key mechanisms of ELCA are ablation and evaporation of tissue by laser. ELCA is expected to prove efficacious in reducing soft tissue such as the culprit coronary lesion of AMI, thrombus in the SVG, or neointima causing ISR, but available data are limited to a small number of cases.[910–912]

8. Bioresorbable Scaffold (BRS)

8.1 Overview

Extraneous material inside the vessel treated by PCI came to be identified as a source of thrombus and inflammation. Eliminating foreign material from inside the treated coronary artery is therefore important. The development of the BRS drew attention because its resorbs completely over time inside the body. The BRS was expected to eliminate arteriosclerosis that occurs from long-term foreign-body reaction as well as the need for DAPT. However, the incidence of both early and late thrombosis with the BRS was higher compared with 2nd-generation and later DES, revealing that longer DAPT was actually necessary with the BRS.

Absorb GT1® (Abbott Vascular Japan) was granted approval in Japan because the BRS had the most reported clinical experience in the country. Subsequently, however, the EU placed restrictions on the use of the device, and the product was discontinued globally. The BRS is now being developed by small manufacturers in small clinical trials. Despite its history, the BRS may have a long-term benefit compared with metal stents that permanently remain in the patient's body and therefore has the potential to be the ideal device for local treatment of CAD.

The BRS is not currently available in Japan. The procedure for BRS placement and reported evidence of the device are discussed next.

8.2 Data on BRS (Bioresorbable Vascular Scaffold [BVS])

The Absorb GT1 BVS by Abbott Vascular Inc. was tested in early safety studies ABSORB Cohort B and EXTEND and then in a number of RCTs (ABSORB II, ABSORB III, ABSORB Japan, ABSORB China, EVERBIO II, and TROFI II), together with registry analysis. During almost 6 years since the product launch in 2011 in Europe, meta-analyses of the early safety studies and pivotal study were published. The risk of repeat revascularization for restenosis with the BVS was similar to that with metal DES, but more frequent device thrombosis was reported for BVS compared with the EES (control).[913,914] A meta-analysis of data collected after 2 years from device placement reported that the repeat revascularization rate was higher for the BVS than for the EES even in the absence of such a difference in analysis of individual study data.[915]

The EES used as the control in these studies has the best clinical outcomes with the least rate of ST. Because the BVS is only the 1st-generation BRS, more time may be necessary for BRS to be able to achieve results similar to those for the EES.

The specific benefit of the BRS is likely to appear only after 5 years or longer when the device has completely resorbed, and such long-term data are still limited. However, multislice CT scans taken 72 months after BRS placement in the ABSORB Cohort B indicated lumen expansion,[916] suggesting the benefit of BRS may be proven when more long-term data become available.

8.3 Recommended Techniques for Reduction of Device Thrombosis

The BRS has thick struts to sustain its structure and overexpansion must be avoided to avoid structural damage. The BRS is also more prone to radial force than metal stents. Like metal stents, insufficient expansion of a BRS can increase the risk of thrombosis. A BRS must be placed with these characteristics in mind in order to reduce thrombosis. It should be noted, however, that careful placement of the device can reduce early thrombosis.[917] The primary challenge is VLST that develops between 1 and 4 years after placement. Strut fracture over time in patients with strut malapposition,[918,919] and development of coronary aneurysms are potential causes of late thrombosis associated with BRS.[920]

Early thrombosis may be caused by technical problems such as edge dissection and insufficient expansion (these are also common with metal stents). Many other factors are suspected, such as large thrombosis volume in patients with dehydration or ACS, and ineffective antiplatelet therapy. Predilatation, Sizing, and Post-dilatation (PSP), known collectively as PSP, are regarded as important for BRS placement. A retrospective analysis indicated fewer events in patients who had BRS placed according to PSP.[921] Previous clinical trials have shown that placing a disproportionately large BRS in a small vessel increases the scaffold footprint and protruded strut, and as a result increases the risk of thrombosis, especially in small vessels with a reference diameter <2.25 mm. Enough strut embedment in the vascular wall is important for early strut coverage by neointima and for reduction of flow disturbance. Japanese clinical trial data indicate that strut embedment was about 50 μm on average, which is shallow compared with the about 80 μm common with metal stents. At only about 50 μm into the vascular wall, the strut remains protruding into the lumen.[922] In a calcified lesion, this embedment depth is difficult to achieve and in such cases malapposition is more likely to occur with a higher

Table 52. Recommendation and Evidence for Intravascular Ultrasound in PCI Guidance

	COR	LOE
IVUS is recommended in complex disease such as LMCA disease, CTO, and diffuse lesions	I	A
IVUS should be considered to optimize stent implantation	IIa	B
IVUS should be considered in ostial lesion, bifurcation lesion, or calcified lesion	IIa	C
IVUS should be considered for reduction of stent thrombosis and restenosis	IIa	C
IVUS is not recommended to determine the indication of PCI based on minimal lumen area or plaque burden	III	C

COR, class of recommendation; CTO, chronic total obstruction; IVUS, intravascular ultrasound; LMCA, left main coronary artery; LOE, level of evidence; PCI, percutaneous coronary intervention.

likelihood of thrombus formation.[923] PSP is deemed important for attaining good strut embedment.

Antiplatelet therapy should be adjusted when ineffective. Compared with clopidogrel, which has a long or inconsistent time to onset of action, new ADP receptor antagonists such as prasugrel and ticagrelor may be more effective and suitable, but evidence supporting them is still lacking. There is only one case report of switching from clopidogrel to ticagrelor after the occurrence of scaffold thrombosis.[924]

If the BRS was covered by neointima 1 year after placement, no subsequent thrombosis was supposed to occur. In reality, however, thrombosis occurring more than 1 year later was reported many times. Many of the patients who had VLST had stopped DAPT entirely, though this is not likely to be the only reason for the occurrence of thrombosis.[915,925,926] The number of patients with malapposition immediately after BRS placement stands out on the list of patients who experienced VLST in the B-SEARCH study conducted in Rotterdam.[927] Long-term (3–4 years) DAPT is probably necessary, at least in patients with poor strut apposition immediately after placement. Thrombosis has also been reported in patients receiving DAPT (aspirin+prasugrel).[919] DAPT may not be able to completely prevent thrombosis associated with strut fracture (scaffold discontinuity revealed by optical coherence tomography [OCT]). Placement of a metal stent to provide support to the scaffold may be necessary in such cases.

Careful selection of lesions and accurate placement are therefore essential for good initial apposition, which is probably the key to achieving long-term survival while preventing VLST. In other words, PSP is also important for reducting the occurrence of VLST.

9. Diagnostic Techniques

9.1 IVUS (Table 52)

IVUS is an imaging technique that uses a catheter inserted into a coronary artery to obtain cross-sectional images of the vessel lumen and arterial wall. Compared with coronary angiography, IVUS allows more accurate assessment of lumen diameter and lumen/vessel area; plaque area, appearance, and distribution; vascular remodeling; coronary artery dissection; ST, and restenosis. IVUS is the most well-established, standard technique among all clinically available intravascular diagnostic imaging techniques.[928] As PCI guidance, IVUS is used to characterize the lesions prior to PCI, determine the suitable stent size, and optimize stent placement. Its findings help select the most appropriate treatment strategy for individual patients.

The percentage of IVUS-guided PCI among all PCI performed in Japan is much higher than in Europe or the USA. Clinical trials have reported controvercial results on the utility of routine IVUS in PCI.[929–931] The benefit of IVUS in PCI has been demonstrated in selected lesions. Clinical trials and meta-analyses have indicated that IVUS guidance improves the outcomes (including survival benefit) of PCI performed on complex disease such as LMCA lesions, CTO, and diffuse lesions.[931–937] The benefit of IVUS for PCI in bifurcation lesions, calcified lesions, and ostial lesions is also suggested.[938,939]

In addition, IVUS may help identify the cause of complications, thrombosis, and restenosis associated with PCI. Minimum stent area and stent edge plaque burden immediately after stent placement are predictors of thrombosis and restenosis.[940,941] However, lumen area and plaque burden at the segment examined under IVUS should not be used to determine the indication of revascularization.

IVUS has its own weakness. It is sometimes difficult to cross extremely tortuous lesions, heavily calcified lesions, severe stenosis, or occlusion with the catheter. IVUS should be used with prior consideration of its suitability for the patient and whether its cost is justified. Interpreting IVUS images also requires knowledge and experience. IVUS for PCI guidance must be conducted under well-established criteria.

Virtual histology IVUS, integrated backscatter IVUS, and near-infrared spectroscopy IVUS all enable automated characterization of plaque components. Whether PCI will benefit from guidance by these techniques awaits for further evaluation in RCTs.

9.2 OCT (Table 53)

OCT and optical frequency-domain imaging (OFDI) obtain luminal images by using near-infrared light and the latest optical technology.[942] An OCT/OFDI system provides a high-resolution image and allows more accurate measurement of lumen diameter or lesion length than angiography or IVUS. It can also differentiate lipid, fibrous tissue, and calcification for characterization of plaque components. Inside arteriosclerotic lesions, OCT/OFDI is capable of identifying plaque rupture/erosion, calcified nodules, thin-cap fibroatheroma, macrophages, cholesterol crystals, vasa vasorum, and thrombi. In PCI, OCT/OFDI offers important information for stent sizing and detects stent underexpansion or malapposition, tissue prolapse, and stent edge dissection more accurately than IVUS. Furthermore, OCT/OFDI has several capabilities that are useful for guiding PCI over IVUS, including automatic measurement, co-registration with angiography (integration of information), construction of 3D images, and automatic detection of stent malapposition.

The benefit of OCT/OFDI guidance on the clinical outcomes of PCI is greater than that of angiography guidance and possibly equal to that of IVUS guidance.[931,943–948] As with IVUS, routine OCT/OFDI in all PCI is not recom-

Table 53. Recommendation and Evidence for OCT/OFDI in PCI Guidance

	COR	LOE
OCT should be considered to optimize stent implantation	IIa	B
OCT should be considered in bifurcation lesion, calcified culprit lesion, or in-stent restenosis	IIa	C
OCT should be considered for reduction of stent thrombosis and restenosis	IIa	C
OCT may be considered in selected patients with chronic kidney disease (excluding hemodialysis) patients	IIb	C
OCT is not recommended in coronary artery ostial lesion or CTO	III	C
OCT is not recommended to determine the indication of PCI based on minimal lumen area or plaque characteristics	III	C

COR, class of recommendation; CTO, chronic total obstruction; LOE, level of evidence; OCT/OFDI, optical coherence tomography/optical frequency domain imaging; PCI, percutaneous coronary intervention.

mended. OCT/OFDI should be used in PCI in select lesions. For bifurcation lesions, OCT/OFDI may help predict side branch occlusion and optimal wire delivery to side branches. In calcified lesions, OCT/OFDI is regarded as useful for assessment of PCI pretreatment such as balloon dilatation or Rotablator® atherectomy. In culprit lesions of ACS, OCT/OFDI assessment of lipid-rich plaque and thrombosis is considered to help predict no-reflow (failure to restore normal myocardial blood flow despite removal of the coronary obstruction) or perioperative myocardial infarction. For ISR, neointimal characterization by OCT/OFDI can purportedly help predict the benefit of DCB.

In addition, OCT/OFDI may help identify the cause of complications, thrombosis, and restenosis associated with PCI. Minimum stent area and lipid-rich plaque at the stent edge immediately after stent placement are indicated as predictors of late repeat revascularization. The degree of neointimal coverage of stent struts, late stent malapposition, and neoarteriosclerosis long after PCI with DES have been suggested to be associated with VLST.

OCT/OFDI also has specific shortcomings. It requires removal of blood from the coronary artery by injection of contrast or low-molecular dextran. Because complete blood removal from the ostia or occluded segment of a coronary artery is difficult, OCT/OFDI is not suitable for imaging of such areas. In patients with spontaneous coronary artery dissection, attention should be paid to the excessive increase in intracoronary pressure associated with injection of contrast agents. OCT/OFDI increases the amount of contrast agent used during catheterization. For patients with CKD (excluding hemodialysis patients), the use of OCT/OFDI should be carefully considered, and if used, appropriate pretreatment to prevent worsening of renal function is necessary. The visible depth of OCT/OFDI is shallow compared with IVUS, making OCT/OFDI only suitable for observation of the plaque surface. OCT/OFDI is therefore unsuitable for quantification of vessel size or plaque area and for assessment of vascular remodeling. Similar to IVUS, the OCT/OFDI catheter may face difficulty crossing highly tortuous or calcified lesions. OCT/OFDI requires training in imaging procedure and interpretation. Prior consideration of the suitability of the procedure and cost-effectiveness are also advised.

Table 54. Recommendation and Evidence for Angioscopy in PCI Guidance

	COR	LOE
Angioscopy may be considered for reduction of stent thrombosis and restenosis	IIb	C
Angioscopy may be considered for reduction of complications of PCI	IIb	C
Angioscopy is not recommended to determine the indication of PCI based on plaque characteristics	III	C

COR, class of recommendation; LOE, level of evidence; PCI, percutaneous coronary intervention.

9.3 Angioscopy (Table 54)

The original angioscopy technique was developed by Mizuno et al[949] in the 1980s, and since then the angioscopy catheter has undergone improvements and been made thinner. The currently used catheter can be delivered to relatively small coronary arteries.[949] Angioscopy produces full-color, high-resolution, three-dimensional images of the lumen to enable macroscopic pathological diagnosis. In Japan, angioscopy was added to the National Health Insurance listing in 2000 and is available in the daily clinical setting.

Historically, angioscopy has made a significant contribution to elucidation of CAD pathology. Angioscopy has been used in examination of various types of CAD, such as ACS, and has shown its effectiveness in detecting thrombosis and yellow plaque.[950] Angioscopy can also detect red thrombi rich in fibrin and red blood cells, white thrombi rich in platelets,[951] and protrusion of yellow tissue from ruptured plaque blocking the lumen together with thrombi in most patients with ACS.[951] Angioscopy may detect yellow plaques occasionally in the culprit lesion of patients with stable effort angina. PCI in such lesions can induce distal embolism by thrombi and the lipid-rich plaque content, which increases the risk of the slow-flow/no-reflow phenomenon and perioperative myocardial infarction. Angioscopy prior to PCI may give information about whether a distal protection device should be used.[951] New-generation DES may show different long-term angioscopic findings compared with the 1st-generation DES. Angioscopy can visualize changes that occur after DES placement.[952] The angioscopic procedure and interpretation of images do require adequate training.

10. Bifurcation Lesions (Table 55)

A bifurcation lesion amenable to PCI is the most frequent type of complex CAD. Accurate assessment of the lesion and the procedure suitable for bifurcation lesions are required to attain favorable outcomes of PCI.

10.1 Lesion Assessment

The Medina classification is the most commonly used classification system for bifurcation lesions.[953] It groups

Table 55. Recommendation and Evidence for PCI in Bifurcation Lesions

	COR	LOE
Stent placement only in the main artery of bifurcation lesion	I	A
Use of IVUS or OCT/OFDI in PCI in bifurcation lesion	IIa	B
2-stent placement when 1 stent is not likely to maintain patency of side branches (considering the angle of those branches or the perfusion area)	IIb	B

COR, class of recommendation; IVUS, intravascular ultrasound; LOE, level of evidence; OCT/OFDI, optical coherence tomography/optical frequency domain imaging; PCI, percutaneous coronary intervention.

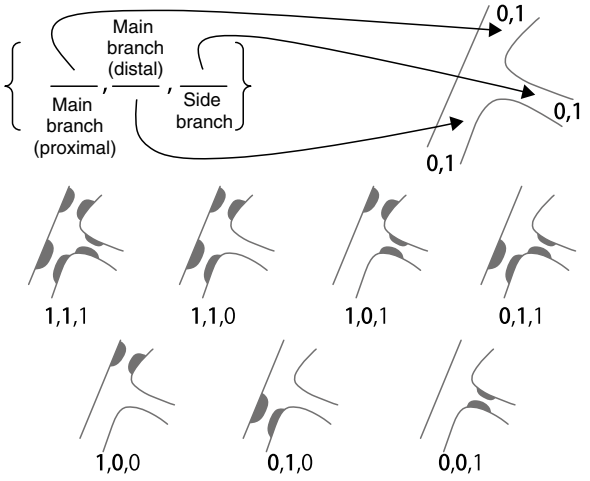


Figure 7. Medina classification of coronary artery bifurcation lesions. (From Medina A, et al. 2006.[953] ©2006 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.)

bifurcation lesions into main branch (proximal), main branch (distal), and side branch combined with "1" for the lesion with stenosis and "0" for the lesion without (**Figure 7**).[953]

In addition to morphology, bifurcation lesions may also be classified by location. For example, a bifurcation lesion in the distal LMCA and another in any other area have different flow demands, vessel diameters, and bifurcation angles, and require careful selection of appropriate technique. The early and mid-/long-term outcomes of PCI also vary between a bifurcation lesion in the distal LMCA and another in any other area.[954]

10.2 Technique

10.2.1 Guidewire for Side Branch

A normal guidewire is not suitable for engaging a side branch oriented in a reverse angle. In such a branch, the guidewire is bent in advance to engage from the distal side (reverse wire technique).[955] There is also a reverse wire technique that uses a double-lumen catheter to facilitate manipulation of the guidewire.[956]

10.2.2 Pretreatment

Some bifurcation lesions with carina shift or plaque shift may require placement of a stent in the side branch. DCA may be used instead to remove plaque and avoid additional stent placement.[957]

10.2.3 Stent Placement

Single stent placement in the main branch achieved superior outcomes compared with 2-stent placement (one in the main branch and another in the side branch) according to a RCT[958] and meta-analyses.[959,960] Whenever feasible, a stent should be placed only in the main branch. If the main branch has a large side branch (≥2.75 mm in diameter) that exhibits severe stenosis, has a large territory, and has a long (≥5 mm) lesion, however, 2-stent placement may be needed and appropriate. There are several types of 2-stent placement methods. Side branch stent placement is performed at the beginning of the procedure for Crush and T-and-protrusion (TAP) stenting. T-stenting and culotte stenting are done in the middle of procedure. The DKCRUSH study indicated 2-stenting has better long-term outcomes, compared with provisional T-stenting, in LMCA disease,[961] but further evaluation (e.g., diagnostic imaging) is needed.

Angiography performed after placing a stent in the main branch sometimes fails to give sufficient information for deciding whether intervention in its side branch is necessary. In such cases, the FFR of the side branch should be useful.[962,963]

10.2.4 Proximal Optimization Technique (POT)

POT is dilatation of the proximal side to the stent in the main branch with a balloon suitable for the particular segment.[964] It helps achieve better apposition of the proximal side of the stent strut to the vascular wall and also makes guidewire delivery to the side branch easier. POT decreases the risk of the guidewire going through the outside of the stent strut when inserting the guidewire in a side branch from the proximal side. In LMCA disease, using POT after placement of a stent to the ostia reduces the risk of deformation of the stent's shape by contact with the guiding catheter.

10.2.5 Re-Engagement With Guidewire in a Side Branch

Where the guidewire is re-engaged in a side branch may affect the degree of subsequent stent expansion. Generally, maximally passing the guidewire distal to the stent strut reduces the likelihood of the strut remaining in the bifurcation, which helps achieve good stent expansion. IVUS and OCT (OFDI) are useful for checking that the wire in the side branch is in the distal side. A three-dimensional OCT image gives an accurate location of the wire,[965] and a double-lumen catheter ensures safe re-engagement of the side branch.

10.2.6 Avoiding Side Branch Occlusion

Placing a stent in the bifurcation can occlude the side branch. Inserting a balloon into the side branch in advance (jailed balloon)[966,967] or inserting a microcatheter into the side branch (Corsair™)[968] are known techniques for reducing the risk of side branch occlusion.

10.2.7 DCB

Because the long-term outcomes of 2-stenting are not always favorable, the DCB is sometimes applied to a side branch

with the hope of decreasing restenosis.[969] However, the long-term effects of DCB use in a side branch remain unclear.

10.2.8 Significance of IVUS

Intravascular imaging provides important information (vessel diameter, plaque distribution, severity of calcification, etc.) for ideal PCI in bifurcation lesions. IVUS is crucial before DCA in a bifurcation LMCA lesion. An optimal stent area has been suggested for LMCA disease. For an LCX lesion, LAD lesion, bifurcation lesion, and LMCA lesion, attaining a stent area of 5 mm^2, 6 mm^2, 7 mm^2, and 8 mm^2, respectively, is considered to minimize the late restenosis risk.[970]

10.3 Outcomes

The long-term outcomes of PCI in bifurcation lesions have improved after the advent of 2nd-generation DES compared with the 1st-generation DES era. Observational studies reported a greater survival benefit of 1st-generation DES with single-stenting than with 2-stenting. With the 2nd-generation DES, however, 2-stenting achieves greater survival benefit than single-stenting.[971,972] The thinner stent struts and improved design of 2nd-generation DES might be contributing to the observed difference in survival benefit.

11. Ostial Lesions

PCI in ostial CAD requires special considerations in assessment of stenosis, techniques to be applied, and long-term outcomes.

11.1 Lesion Assessment

IVUS should prove useful for assessment of an ostial lesion when angiography alone is insufficient for thorough assessment.[973] For PCI in an ostial RCA lesion, catheter insertion might cause coronary spasm. Adequate vasodilator must be administered before assessment of stenosis. For a moderate (about 75%) ostial stenosis, assessment of myocardial ischemia using FFR or iFR is also useful.

11.2 Technique

Positioning of a stent constitutes the critical part of PCI in ostial RCA lesions. Selecting a suitable angiographic angle for the ostia or marking the intended stent location on the IVUS image will make stent placement easier. Also, IVUS should be used to characterize the lesion and to select the optimal sized stent.[973]

11.3 Outcome

The restenosis rate of ostial RCA lesions is higher than that of other ostial lesions. Stent fracture or recoiling caused by mechanical stress is a potential cause of restenosis of ostial RCA lesions.[430,974] Intervention in ISR of the RCA is frequently followed by recurrent restenosis,[975] which makes the initial PCI more important for reducing restenosis. Ostial LMCA lesions have a lower restenosis rate compared with other ostial lesions.

The restenosis rate of ostial lesions with 2nd-generation DES is lower than with 1st-generation DES.[976,977]

Table 56. Recommendation and Evidence for PCI in CTO

	COR	LOE
Assessment of the difficulty of PCI in CTO lesion using J-CTO score	IIa	B
PCI in CTO in viable myocardium when angina persists despite medical therapy	IIb	B
PCI in CTO of an artery supplying a small territory	III	C

COR, class of recommendation; CTO, chronic total occlusion; J-CTO, Multicenter CTO Registry of Japan; LOE, level of evidence; PCI, percutaneous coronary intervention.

12. CTO (Table 56)

CTO is defined as "TIMI 0 flow with an occlusion duration ≥3 months or unknown",[978,979] and is seen in about 20% of CAD patients who undergo angiography.[980,981]

12.1 Lesion Assessment

PCI is considered when the patient has viable and ischemic myocardial segments supplied by a CTO and has persistent angina symptoms associated with the CTO despite medical therapy. PCI in a CTO lesion requires accurate assessment of the lesion and good PCI skills for successful outcome.[982] The difficulty of PCI in a CTO lesion can be estimated using the J-CTO score (sum of scores in 5 predictors) (**Table 57**).[983]

12.2 Technique

The wiring techniques include the following: (1) Antegrade wire escalation, (2) parallel wire technique, (3) IVUS guidance, (4) direct retrograde wire crossing, (5) kissing wire technique with bidirectional approach, (6) controlled antegrade and retrograde tracking (CART), and (7) reversed CART.

The choice of technique to be used will be based on the length of the CTO lesion, location and morphology of the proximal end of the CTO, characteristics of arteries in the distal side of the CTO (diameter, stenosis, calcification, side branch at the distal end of CTO), and whether the artery with the CTO has collateral circulation that allows a retrograde approach. When the chosen technique is deemed unsuitable during PCI, switching to another novel technique increases the chance of success and reduces complications.[984] The success rate of PCI in CTO lesions is still low when severe calcification is present.[984]

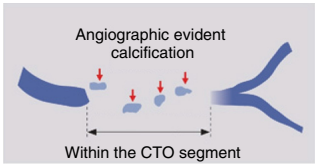
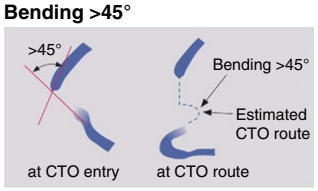
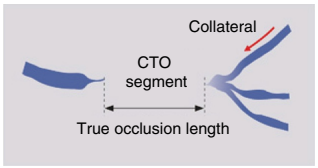
12.3 Outcomes

12.3.1 Short-Term

The reported rates of in-hospital mortality range from 0.2% to 0.9% and the incidence of MACCE, including serious coronary artery perforation, is 2–7.0%.[863,985,986] Patients with successful PCI in CTO lesions have significantly lower rates of in-hospital death and MACCE compared with those with unsuccessful PCI (0.5% vs. 1.4%[987] and 2.4–5.7% vs. 7.7–10.2%, respectively[985–987]).

Retrograde approach, advanced age, and disease complexity (based on J-CTO score) have been noted as predictors of complications.[986,988] The retrograde approach is correlated with significantly more frequent symptomatic ischemia and asymptomatic myocardial injury compared

Table 57. J-CTO Scoring System (for Chronic Total Occlusion)

Variables and definitions		
Tapered **Blunt** 	Entry with any tapered tip or dimple indicating the direction of true lumen is categorized as "tapered"	Entry shape ☐ Tapered (0) ☐ Blunt (1) Point
Calcification 	Regardless of severity, 1 point is assigned if any evident calcification is detected within the CTO segment	Calcification ☐ Absence (0) ☐ Presence (1) Point
Bending >45° 	1 point is assigned if bending >45° is detected within the CTO segment. Any tortuosity separate from the CTO segment is excluded from this assessment	Bending >45° ☐ Absence (0) ☐ Presence (1) Point
Occlusion length 	Using good collateral images, try to measure the "true" distance of the occlusion, which tends to be shorter than the first impression	Occlusion length ☐ <20 mm (0) ☐ ≥20 mm (1) Point
Re-try lesion Is this a re-try (2nd attempt) lesion (previously attempted but failed)?		Re-try lesion ☐ No (0) ☐ Yes (1) Point
Category of difficulty (total points) ☐ Easy (0) ☐ Intermediate (1) ☐ Difficult (2) ☐ Very difficult (≥3)		Total Point

CTO, chronic total occlusion; J-CTO, Multicenter CTO Registry of Japan. (From Morino Y, et al. 2011.[983] Copyright (2011) by the American College of Cardiology, with permission from Elsevier. https://www.sciencedirect.com/journal/jacc-cardiovascular-interventions.)

with the antegrade approach (13.8% vs. 6.7%). In patients who experienced symptomatic ischemia and asymptomatic myocardial injury, the incidence of MACE was significantly higher over a follow -up period of 2.3 years.[989]

PCI in CTO lesions requires a higher dose of contrast agent, higher radiation exposure (air kerma), and longer procedure with longer fluoroscopy time compared withPCI in any other type of lesion. The median dose of contrast, radiation exposure, length of procedure, and fluoroscopy time are respectively 270 mL, 2.9 Gy, 123 min, and 47 min[986] for all PCI in CTO lesions. The amount of contrast, radiation exposure time, length of procedure, and fluoroscopy time are all significantly higher/longer in unsuccessful procedures than in successful procedures.[985]

12.3.2 Long-Term

The presence of a CTO lesion is a risk factor for incomplete revascularization in PCI. Incomplete revascularization has been frequently reported to affect survival.[199] A successful PCI in a CTO lesion can decrease all-cause death and MACE,[990–992] improve LVEF, and decrease left ventricular endsystolic volume.[993,994] Compared with OMT, PCI alleviated angina symptoms, reduced exercise intolerance, and improved QOL for up to 3 years but showed little benefit in mortality, myocardial infarction, stroke, or repeat revascularization, revealing no prognostic benefit.[995]

Although technical improvements have raised the success rate of PCI in CTO lesions, the outcomes of the procedure still depend much on the operator's experience and skill. Because of the shortage of studies comparing PCI in CTO lesions with other treatments, the relative applicability and effectiveness of PCI vs. other treatment options have not been fully investigated.

VIII. CIN

1. Diagnosis

A diagnosis of CIN is made when "SCr is increased ≥0.5 mg/dL or ≥25% from baseline within 72 h after iodinated contrast administration".[996] Alternatively, the KDIGO Clinical Practice Guideline for Acute Kidney Injury may be used[997,998] for diagnosis. The following precautions apply: (1) assessment of renal function using the last available SCr prior to contract administration and (2) use of the eGFR in the baseline renal assessment but changing to SCr for diagnosis of CIN.

2. Risk Evaluation

Some risk factors for CIN after CABG/PCI have been reported, but are not fully validated.[999] The risk factors should therefore only be used as reference. **Table 58** presents the risk factors for CIN listed in the "Guidelines for iodinated contrast administration in patients with kidney disease 2018" published by the Japanese Society of Nephrology and others.[1000]

The osmotic pressure of contrast agent has been debated as a potential cause of CIN. However, no difference in the incidence of CIN has been reported between isotonic and hypotonic contrast media. In addition, the reported incidence of CIN is similar among hypotonic contrast media. Nevertheless, a higher incidence of CIN has been indicated for intraarterial administration than intravenous administration.

While PCI is not shown to worsen the prognosis of CKD, contrast media should nevertheless be kept to a necessary minimum. Also, repeating PCI within a short period of time should be avoided.

3. Prophylaxis

Patients with CIN reportedly have a higher incidence of cardiovascular events, which makes preventing CIN a priority. However, hydration is the only recommended prophylactic treatment supported by evidence.[1001,1002]

In patients undergoing elective PCI, normal saline should be administered at 1 mL/kg/h from 6 h before contrast administration. After the end of contrast-enhanced imaging, saline should be administered at 1 mL/kg/h for 6–12 h. When the time available for hydration is limited, the use of sodium bicarbonate solution is also recommended. In patients undergoing emergency PCI, infusion of sodium bicarbonate should be given at 3 mL/kg/h from 1 h before contrast administration and at 1 mL/kg/h for 6 h after contrast-enhanced imaging. Hydration by drinking alone is not sufficient. Appropriate hydration therapy should be administered.

A number of drugs, such as N-acetylcysteine, h-ANP, ascorbic acid, and statins, have been tested for prophylaxis of CIN, but none has shown favorable results.

Hemodialysis is also occasionally administered, but it has no demonstrated prophylactic effect and should be avoided.[1003,1004]

4. Treatment

For the treatment of CIN, loop diuretics, low-dose dopamine, and hANP have no evidence of efficacy. Also, hydration therapy should be avoided when the patient shows no reduction in effective circulating plasma volume. Continuous hemofiltration is recommended for patients with poor performance status (e.g., with oliguria), but not for improvement of renal dysfunction.

Refer to the "Guidelines for iodinated contrast administration in patients with kidney disease 2018" edited by the Japanese Society of Nephrology, Japan Radiological Society, and Japanese Circulation Society[1000] for more information about the treatment of CIN.

Table 58. Risk Factors for CIN

Factor	Description/guidance
CKD	Risk factor for CIN onset
Advanced age	Risk factor for CIN onset
Diabetes mellitus	Risk factor for CIN when the patient has CKD; otherwise may or may not be a risk factor
Use of RAS inhibitor	No clear evidence whether it increases the risk of CIN onset
Continued use of diuretics	No evidence whether it increases the risk of CIN onset
Prophylactic diuretics	Not recommended
NSAIDs	Not recommended
Antidiabetic biguanides	Appropriate action (e.g., interruption) should be taken
Patients on peritoneal dialysis	May adversely affect residual renal function
Having only 1 kidney	No clear evidence whether it increases the risk of CIN onset

CIN, contrast induced nephropathy; CKD, chronic kidney disease; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin–angiotensin system. (From Japanese Society of Nephrology, et al. 2018.[1000])

IX. Perioperative Medical Therapy

1. PCI

The chapter on antithrombotic therapy was revised in 2020. For details, please refer to the "JCS 2020 Guidelines focused update on antithrombotic therapy in patients with coronary artery disease", edited by the JCS.

1.1 Concomitant Medical Therapy (Table 59)

Anticoagulation therapy is required to prevent thrombotic complications during PCI. In Japan, however, unfractionated heparin is the only anticoagulant used, whereas in Europe/USA, other anticoagulants such as the direct antithrombin bivalirudin and low-molecular heparin enoxaparin are available. Intravenous glycoprotein IIb/IIIa inhibitors are also not approved for use in Japan.

1.1.1 Unfractionated Heparin

The activated clotting time (ACT) is used to measure the effects of heparin. Unfractionated heparin should be administered as appropriate[1005,1006] to keep ACT between 250 and 400 s. Increased hemorrhagic complications are reported when the ACT >400 s during PCI.[1007] An initial bolus injection of 70–100 IU/kg should be administered after arterial sheath insertion. An additional 2,000–5,000 IU should be administered when the ACT does not achieve the target range.

Heparin-induced thrombocytopenia (HIT) is a known adverse reaction, other than bleeding, to heparin treatment. HIT is suspected if thromboembolism occurs during heparin administration or thromboembolism of unknown origin develops following heparin treatment.

1.1.2 Argatroban

Argatroban has been reported as effective for the treatment of HIT[1008,1009] and its use as treatment is covered by the National Health Insurance in Japan. When HIT occurs or is suspected, administer 100 μg/kg of argatroban as a bolus over 3–5 min, followed by infusion at 6 μg/kg/min. Measure the ACT after about 10 min and adjust the infusion rate to control the ACT between 250 and 400 s. When continued anticoagulation therapy is desired after PCI, decrease the argatroban infusion rate to 0.7 μg/kg/min to adjust the activated partial thromboplastin time to between 1.5- and 3-fold the reference value. Argatroban is metabolized by the liver, so a lower dose should be considered in patients with hepatic impairment.

Table 59. Recommendation and Evidence for Medical Therapy During PCI

	COR	LOE
Administer unfractionated heparin during PCI to control ACT between 250 and 400 s	I	B
Administer argatroban for the treatment of HIT	I	B

ACT, activated clotting time; COR, class of recommendation; HIT, heparin-induced thrombocytopenia; LOE, level of evidence; PCI, percutaneous coronary intervention.

1.2 DAPT (Table 60)

DAPT has been standard treatment after stent placement since the establishment of the efficacy of aspirin + thienopyridine antiplatelet for ST prophylaxis in a group of clinical trials including the STARS study.[1010]

1.2.1 DAPT Drugs and Duration

Initially, the duration of DAPT used to be lengthy after PCI with 1st-generation DES, because of concerns about delayed re-endothelialization at the stented site. A j-Cypher registry study in Japan indicated that, although ceasing thienopyridine within 6 months increased the risk of ST, ceasing it more than 6 months after PCI did not increase the cardiac event risk over 2 years.[1011] Even when thienopyridine was continued for >1 year, VLST and cardiovascular events were not decreased in frequency over 5 years.[1012] The ISAR-SAFE study,[1013] ITALIC study,[1014] and SECURITY study,[1015] which compared 6-, 12-, and 24-month DAPT, respectively, as well as the Japanese NIPPON study[1016] failed to demonstrate the efficacy of long-term DAPT. The typical length of DAPT became shorter after 2nd-generation and later DES were shown to decrease ST compared with 1st-generation DES.[1017]

The ACC/AHA guidelines in 2012 and the ESC/EACTS guidelines in 2018 recommend aspirin+≥6 months of clopidogrel to prevent ST in patients with stable CAD and a low risk of bleeding, and aspirin + 1–3 months of clopidogrel in patients with stable CAD and a high risk of bleeding.[1018,1019] The NIPPON and STOPDAPT studies conducted in Japan also reported that shorter DAPT does not increase ST or cardiovascular events.[1020] No inhibitory effect of ≥1-year DAPT on cardiac events was found in subgroup analysis of patients with DM, myocardial infarction, or highly complex CAD.[1021,1022] A Japanese observational study reported that prolonged DAPT increased moderate or severe bleeding requiring transfusion.[1023] For patients at high bleeding risk, stopping DAPT early should

Table 60. Recommendation and Evidence for DAPT in PCI

	COR	LOE
Aspirin 162–200 mg before PCI and subsequently 81–100 mg/day in patients not treated with aspirin	I	A
Aspirin + ADP receptor ($P2Y_{12}$) inhibitor for ≥6 months after stent placement	I	A
Loading dose of either prasugrel 20 mg or clopidogrel 300 mg before stent placement in patients not treated with $P2Y_{12}$ inhibitor	IIa	C
Discontinue DAPT within ≤3 months in patients at increased bleeding risk	IIa	B
Continue DAPT for up to 30 months in patients with high ischemic risk and no bleeding events in the first 6 months of DAPT	IIb	B
Thienopyridine antiplatelet monotherapy in patients with aspirin contraindication	IIb	B
Ticagrelor + aspirin when neither clopidogrel nor prasugrel is appropriate	IIb	B

ADP, adenosine diphosphate; COR, class of recommendation; DAPT, dual antiplatelet treatment; LOE, level of evidence; PCI, percutaneous coronary intervention.

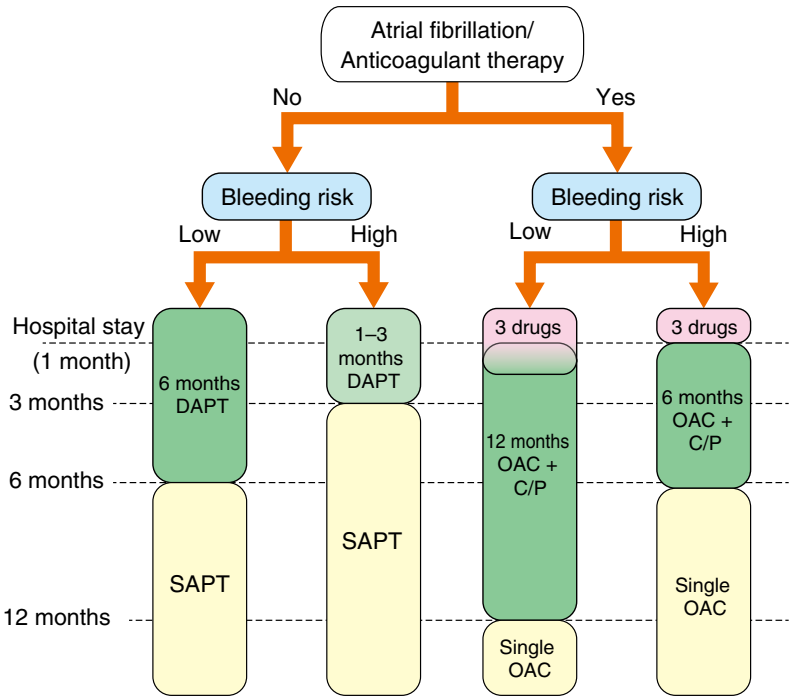


Figure 8. Antithrombotic therapy after percutaneous coronary intervention. C/P, clopidogrel/prasugrel; DAPT, dual antiplatelet treatment; OAC, oral anticoagulant; SAPT, single antiplatelet therapy.

Table 61. PRECISE-DAPT and DAPT Scores

	PRECISE-DAPT score	DAPT score
Timing	After stent placement	After 12 months of DAPT
Length of DAPT	Short (3–6 months) vs. Standard/Prolonged (12–24 months)	Standard (12 months) vs. Prolonged (30 months)
Score factors	Hemoglobin, WBC count, age, creatinine clearance, history of bleeding	Age, smoking, diabetes mellitus, PCI on myocardial infarction, History of PCI or myocardial infarction, paclitaxel-eluting stent, <3 mm stent diameter, heart failure or LVEF <30%, stented venous graft
Score range	0 to 100	–2 to 10
Recommended cutoff value	≥25 → Short DAPT <25 → Standard/Prolonged DAPT	≥2 → Prolonged DAPT <2 → Standard DAPT
Web calculator	www.precisedaptscore.com	www.daptstudy.org

DAPT, dual antiplatelet treatment; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; WBC, white blood cell. (From Costa F, et al. 2017[1024] and Yeh RW, et al. 2015.[1025])

be considered, even within 3 months, to avoid bleeding events. The optimal duration of antiplatelet therapy may vary by race and generation of DES.

Nevertheless, we adopt similar recommendations on the duration of DAPT based on bleeding risk in stable CAD to those presented in European and American guidelines (**Figure 8**). The DAPT drug and duration recommendations were further updated in the "JCS 2020 Guideline focused update on antithrombotic therapy in patients with coronary artery disease" (see guidelines for details).

1.2.2 Measures of Bleeding Risk

Outside Japan, useful tools have been developed for calculation of the optimal duration of DAPT (**Table 61**).[1024,1025] For example, the RECISE-DAPT score is the measure of bleeding risk during DAPT after PCI based on the patient's age, history of bleeding, whote bllod cell count, hemoglobin, and Cr clearance.[1024] The DAPT score is a measure of long-term bleeding risk. A higher score is assigned to patients who smoke, have DM, have a history of myocardial infarction and/or PCI, have a paclitaxel-eluting stent, have a stent smaller than 3 mm in diameter, have HF or LV ejection fraction <30%, or have a stented venous graft. Higher age decreases the DAPT score. In patients with a high DAPT score, long-term DAPT can decrease mortality and cardiovascular events such as myocardial infarction and stroke without increasing the bleeding risk.[1024,1025] Caution should be exercised when applying these scores to Japanese patients.

Recently, Japanese researchers developed a measure of bleeding risk and ischemic event risk based on an analysis of the CREDO-Kyoto registry.[1026] The percentage of

Table 62. Recommendation and Evidence for Antithrombotic Therapy in PCI in Patients on Anticoagulants

	COR	LOE
Triple antithrombotic therapy after stent placement	I	C
Triple antithrombotic therapy (for 3–6 months) after stent placement in patients with high ischemic risk	IIa	B
Triple antithrombotic therapy (for <1 month) after stent placement in patients with high bleeding risk	IIa	B
DOAC over warfarin as anticoagulant	IIa	B
Switch to a single anticoagulant from 1 year after stent placement	IIa	B
When warfarin is used, set a low target PT/INR range and control TTR at ≥65%	IIb	C

COR, class of recommendation; DOAC, direct oral anticoagulant; INR, international normalized ratio; LOE, level of evidence; PCI, percutaneous coronary intervention; PT, prothrombin time; TTR, time in therapeutic range.

Table 63. Predictors of Stent Thrombosis

History of stent thrombosis while on adequate antiplatelet therapy
First-generation DES
Non-ST-segment elevation or ST-segment elevation myocardial infarction
Complex PCI (placement of ≥3 stents, treatment of ≥3 lesions, 2 stents in bifurcation lesion, ≥60 mm total stented length, or chronic total occlusion)
Diffuse lesion in diabetic patients
Chronic kidney disease

DES, drug eluting stent; PCI, percutaneous coronary intervention. (From Roffi M, et al. 2016[1035] and Giustino G, et al. 2016.[1036])

Table 64. Management of Bleeding Risk in PCI Patients on Anticoagulation Therapy

Assess ischemic/bleeding risk
Keep triple therapy as short as possible; dual therapy after PCI to be considered
For patients treated with warfarin, consider a target PT/INR in the lower part of the recommended range and control TTR at ≥65%
Concomitantly administer proton-pump inhibitor whenever possible
Perform PCI via radial artery access if feasible

INR, international normalized ratio; PCI, percutaneous coronary intervention; PT, prothrombin time; TTR, time in therapeutic range. (From Valgimigli M, et al. 2018.[1019])

patients with a bleeding risk accurately assessed by these measures was not more than 0.7.[1024–1026] The basic strategy is to individualize the DAPT duration based on the balance between bleeding and ischemic risks, but many bleeding risk factors are also risk factors for ischemic events. Therefore, the treating doctor should consider the various risks globally and adopt these indicators.

In the "JCS 2020 Guideline focused update on antithrombotic therapy in patients with coronary artery disease", the concept of high bleeding risk was adopted (see the 2020 guidelines for details).

1.3 Patients on Anticoagulant Therapy (Table 62)

Patients with persistent or paroxysmal AF need anticoagulation therapy.[1027] With the prolongation of life expectancy, PCI in patients with AF is becoming more common and is estimated to account for about 10% of all PCI.[1028,1029] Immediately after stent placement, such patients need triple antithrombotic therapy comprising DAPT (aspirin + thienopyridine antiplatelet) and anticoagulant (warfarin or direct oral anticoagulant [DOAC]) to balance between bleeding and thromboembolism.

1.3.1 Overseas Evidence and Recommendations

The WOEST study compared safety and efficacy between dual agent therapy (warfarin + single antiplatelet) and triple agent therapy (warfarin+DAPT) in PCI patients requiring oral anticoagulation therapy. The dual agent group was reported with less frequent bleeding events and had a lower incidence of composite cardiovascular events compared with the triple agent group.[1030] The PIONEER AF-PCI study compared dual therapy (rivaroxaban 15 mg + clopidogrel) with the more conventional triple therapy (warfarin + DAPT) and reported a significantly lower incidence of bleeding events in the dual agent group, although little difference was seen in the efficacy endpoints.[1031] Similar findings were reported by the RE-DUAL PCI study of dabigatran.[1032]

Single DOAC + clopidogrel can significantly decrease bleeding events, without increasing thrombotic events or repeat revascularization, compared with the more conventional warfarin + DAPT. The ESC/EACTS guidelines in 2018 recommended triple therapy for 6 months in patients at high ischemic risk, for 1 month in patients with low bleeding risk, and dual therapy instead (single DOAC + clopidogrel) in patients with high bleeding risk.[1019] A recent expert report by the AHA recommended triple therapy (single DOAC+DAPT) for no more than 1 month after PCI.[1033] The European Heart Rhythm Association (EHRA) recommends triple therapy during hospital stay for elective PCI with new-generation DES followed by dual therapy (DOAC+clopidogrel) after discharge. For patients who undergo PCI for ACS, the EHRA recommends triple therapy for ≤3 months followed by DOAC+clopidogrel.[1034]

1.3.2 Recommendations and Precautions in Japanese Patients

Triple therapy administered for a reasonable period of time in non-Japanese patients is likely to be also effective in Japanese patients. Considering device improvements over the years and the increasing prevalence of AF among older patients who undergo PCI, however, in this guideline we recommend limiting triple therapy to no more than 1 month and generally to the duration of hospital stay after PCI (**Figure 8**). In patients at increased thrombotic risk, triple therapy should be extended to 3–6 months. In patients at risk of bleeding, dual therapy should be given for no more than 6 months.

The ESC/EACTS guidelines present cases of complex PCI where early interruption of triple therapy is difficult due to the risk of ST. These cases give predictors of ST that should prove useful for deciding the duration of triple therapy in Japanese patients (**Table 63**).[1035,1036] PCI requires caution to avoid hemorrhagic complications and a PCI

Table 65. Recommendation and Evidence for Anticoagulant Therapy in CABG

	COR	LOE
Initiation of unfractionated heparin/ low-molecular heparin + oral anticoagulation therapy, as soon as postoperative bleeding risk has subsided, in patients amenable to anticoagulation therapy (history of atrial fibrillation, embolism)	I	C
Initiation of unfractionated heparin/ low-molecular heparin and oral anticoagulation therapy in patients who have postoperative atrial fibrillation for ≥12 h	I	B
Anticoagulation therapy intended to improve graft patency after CABG/OPCAB in patients not amenable to anticoagulants	III	A

CABG, coronary artery bypass grafting; COR, class of recommendation; LOE, level of evidence; OPCAB, off-pump coronary artery bypass grafting.

Table 66. Recommendation and Evidence for Antiplatelet Therapy in CABG

	COR	LOE
Start oral aspirin (81–162 mg/day) within 48 h after CABG/OPCAB	I	A
DAPT after CABG/OPCAB in patients with acute coronary syndrome	I	A
DAPT after OPCAB to keep venous graft patency in patients with exertional angina	IIa	B
Continuation or initiation of preoperative oral aspirin in patients with elective CABG/OPCAB	IIa	C
Add an antiplatelet to aspirin before CABG to improve the surgical outcome (including postoperative patency)	III	B

CABG, coronary artery bypass grafting; COR, class of recommendation; DAPT, dual antiplatelet treatment; LOE, level of evidence; OPCAB, off-pump coronary artery bypass.

strategy that does not require prolonged DAPT should be adopted (**Table 64**).[1019]

The AFIRE study was conducted in Japanese patients with nonvalvular AF and stable CAD. Our expert opinion is single anticoagulant therapy from at least 12 months after stent placement in stable CAD patients with nonvalvular AF (**Figure 8**).

The approved dose of prasugrel in Japan is approximately one-third that used overseas. At present, there is insufficient evidence for the combination of prasugrel and anticoagulant therapy in Japanese patients. We need more evidence to recommend this combination therapy.

2. CABG

2.1 Anticoagulants (Table 65)

Anticoagulants are not recommended for oral treatment after CABG unless the patient has indications for anticoagulation therapy (e.g., AF). A RCT investigated the effects of routine warfarin use in CABG patients and revealed a significant increase in postoperative bleeding risk. On the effect of warfarin on venous graft patency, however, the reported evidence is contradictory.[1037–1039] A meta-analysis of data from these studies with mixed results indicated that warfarin monotherapy can significantly increase graft patency rate and that the extent of this benefit is similar to that of aspirin.[1040] However, because aspirin has lower bleeding risk, it has been the first-line drug for maintenance of graft patency after CABG.

The effects of adding warfarin to aspirin were investigated in a RCT (Post CABG study). The study assigned 1,351 patients to aspirin + warfarin or aspirin + placebo and reported no significant difference in graft patency rate,[1041] concluding that combining aspirin with warfarin is not recommended. However, the Post CABG study only used low-dose warfarin (mean prothrombin time-international normalized ratio [PT-INR] of 1.4). The efficacy of warfarin for a target PT-INR range of 1.6–2.6 or ≥2.0 is unclear. A study comparing aspirin + warfarin with aspirin alone after myocardial infarction reported a significantly lower incidence of cerebral infarction and myocardial infarction in patients treated with aspirin and warfarin (PT-INR ≥2.0). The effects of the aspirin + warfarin combination therefore need further analysis.[1042]

The effects of DOAC administered after CABG have been investigated in a few RCTs and also remain unclear.

When AF occurs after CABG, anticoagulation therapy is recommended for prevention of cerebral infarction.[1043] At exactly what time point heparin and or OAC should be started after the occurrence of AF is not established. Timing for treatment initiation is decided by weighing the patient's risk for bleeding against the risk of embolism, but 12–48 h after onset is most common.

2.2 Antiplatelet Drugs (Table 66)

Multiple benefits of aspirin administered after CABG have been frequently reported.[1044–1047] Lifelong aspirin therapy is recommended because it has been shown to increase venous graft patency, improve post-CABG survival, and decrease postoperative events. In a RCT in 407 patients, oral aspirin + dipyridamole improved the 1-year patency rate of venous grafts compared with patients without such treatment (89% vs. 77%).[1047] On the other hand, for patients with an ITA graft, aspirin does not help increase graft patency because of the high patency rate of ITA grafts even without aspirin.[1048] However, aspirin is today's standard therapy for secondary prophylaxis (together with its benefit on native coronary artery lesions) after CABG, because an increased survival rate to 68% and a decreased incidence of myocardial infarction by 48% were reported in patients treated with aspirin in another study.[1049]

Varying reports have also been published about the timing of oral aspirin initiation. A report indicated aspirin started before CABG decreased perioperative complications and mortality, and concluded that aspirin should be initiated before CABG/OPCAB.[1050] Aspirin started at least 3 days after CABG was found to show no benefit on graft patency.[1037,1038,1051] Aspirin's benefit on graft patency was reported when the drug was started within 6 or 7 h after CABG.[1047,1052] In another report, aspirin started within 48 h after CABG significantly decreased early postoperative mortality, myocardial infarction, stroke, and renal failure without affecting postoperative bleeding. The commonly recommended timing for initiation of oral aspirin therapy is within 48 h after CABG.[1049] With regard to aspirin dose, Fremes et al performed a meta-analysis and noted 100–325 mg/day compared with 975 mg/day maintained the benefit on graft patency without increased bleeding.[1040] The

commonly recommended aspirin dose is 81–325 mg/day in Europe and the USA.[1053] Aspirin 81–162 mg/day is recommended for prophylaxis of recurrent myocardial infarction in Japanese patients with chronic angina. Our recommended dose is also 81–162 mg/day, considering the average Japanese build and susceptibility to bleeding.

Combining aspirin with another antiplatelet drug in DAPT, when administered before CABG/OPCAB, significantly increases postoperative bleeding while failing to decrease postoperative MACE.[529–531] DAPT after CABG/OPCAB is indicated in patients with ACS. Benefits of DAPT were demonstrated in RCTs that compared aspirin alone with aspirin + clopidogrel after revascularization in ACS patients (CURE study, CREDO study).[1054,1055] In the CURE study where CABG was performed in some patients, the DAPT group was reported with significantly less frequent cardiovascular mortality, myocardial infarction, and stroke. DAPT is therefore recommended after CABG/OPCAB in ACS patients. The efficacy of DAPT for stable angina after CABG/OPCAB has also been assessed in some RCTs.[1056–1058] A meta-analysis of data from those studies showed that DAPT significantly improved venous graft patency compared with aspirin alone and also that DAPT after OPCAB was more efficacious than after CABG.[1059,1060] In addition, DAPT may possibly inhibit progression of native CAD.[1061,1062]

2.3 Lipid Control Agents (Table 67)

Patients with high levels of LDL cholesterol (LDL-C) are at increased risk of atherosclerotic disease and intimal hyperplasia in venous graft after CABG/OPCAB.[1063,1064] Statins are HMG-CoA reductase inhibitors and an essential treatment after CABG, because they can inhibit venous graft occlusion and intimal hyperplasia,[726,1041,1065–1067] decrease cardiovascular events, improve survival rate, and act against progression of native CAD.[1068–1071] Resumption of statin therapy early after surgery is effective and recommended.[1072–1074] For patients who are unable to take statins orally, fibrates are a viable alternative. Fibrates act on HDL cholesterol and triglycerides, but little evidence shows therapeutic benefits after CABG. Nevertheless, a study reported fibrates administered without statins decreased new lesions in venous grafts.[1075] Statins share the same benefit, which exceeds that of fibrates, hence are the first-line treatment. The statin + fibrate combination increases complications (rhabdomyolysis, myopathy, etc.) and is not recommended. The effects of the combination therapy administered after CABG are unknown.[1076,1077] Statins also have diverse benefits not mediated by control of LDL-C. These include enhancement of vascular endothelial function, inhibition of vascular smooth muscle cell proliferation, plaque stabilization, and inhibition of inflammatory response and platelet aggregation.[1078–1082] In the USA, high-dose statin therapy (either atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) is recommended after CABG/OPCAB in patients ≤75 years. Although medium-dose statin therapy is recommended for patients >75 years elsewhere, both the indicated medium-dose and high-dose levels in Europe/USA are excessive, and lower doses are used in Japanese patients.

Lower LDL-C levels are associated with more potent inhibition of native CAD. For secondary prophylaxis in high-risk patients (e.g., after CABG), ≤70 mg/dL is desirable.[1083–1085] Relatively few RCTs have focused on the effects of LDL-C levels on graft patency rate after CABG. The Post CABG study randomized patients to lovastatin 40–80 mg/day or 2.5–5 mg/day to investigate the effects of high-dose statin therapy and reported a significantly lower LDL-C in the high-dose group (93–97 mg/dL vs. 132–136 mg/dL, P<0.001), a significantly lower percentage of venous graft occlusion on angiography 4 years later (10% vs. 21%, P<0.001), and a smaller number of diseased grafts (27% vs. 39%, P<0.001).[1041] Cardiovascular events were also less frequent in the high-dose group, supporting <100 mg/dL as the LDL-C threshold and high-dose statin therapy. Hata et al reported less yellow plaque inside venous grafts in patients with <80 mg/dL LDL-C and suggested a lower LDL-C threshold is desirable.[1086] Based on recent discoveries that lowering LDL-C levels significantly decreases cardiac events (together with the benefit of a low LDL-C against native CAD), today's recommended LDL-C target is ≤70 mg/dL.[1083–1085]

Combining the intestinal cholesterol absorption inhibitor ezetimibe with statin can lower LDL-C and vascular events more than statin alone and is a viable option when statin alone cannot lower LDL-C sufficiently.[118,1087] The efficacy of the PCSK9 inhibitor evolocumab in combination with statin against arteriosclerotic disease was recently reported, but there is little evidence yet of the efficacy of evolocumab used after CABG.[119]

Progression of native CAD occurs even in patients with low HDL-C or high triglycerides.[1088] Smoking cessation, exercise therapy, and diet therapy are also indicated for such patients.

2.4 Other Drugs, Including BB (Table 68)

Oral BB therapy before and after CABG is recommended for prophylaxis of perioperative AF.[1089–1093] BB + ACE-I is recommended for patients with impaired cardiac function or a history of myocardial infarction. The efficacy of the combination therapy for lowering long-term mortality and HF has been indicated in a number of reports.[1094–1097]

Table 67. Recommendation and Evidence for Statins After CABG/OPCAB

	COR	LOE
Statin (excluding in patients who have contraindications to statins)	I	A
Use of intestinal cholesterol absorption inhibitor together with statin when statin alone is unable to control LDL cholesterol	IIa	B

CABG, coronary artery bypass grafting; COR, class of recommendation; LDL, low-density lipoprotein; LOE, level of evidence; OPCAB, off-pump coronary artery bypass.

Table 68. Recommendation and Evidence for BB and ACE-I Use in Coronary Artery Bypass Grafting

	COR	LOE
BB for prophylaxis of postoperative atrial fibrillation	I	A
BB + ACE-I in patients with impaired cardiac function or a history of myocardial infarction	I	B

ACE-I, angiotensin converting enzyme inhibitor; BB, beta-blocker; COR, class of recommendation; LOE, level of evidence.

X. Volume-Outcome Relationship of PCI and CABG in Japan

1. PCI

The 2011 ACCF/AHA/SCAI guideline was the first to include clear-cut operator/institutional criteria regarding the volume–outcome relationship of PCI (Class I recommendation, Level of evidence C, for PCI at an institution with ≥400 procedures per year and an operator(s) performing ≥75 procedures per year).[1098] The threshold has been later lowered due to improved safety of PCI and device improvements. The revised ACCF/AHA/SCAI guideline in 2013 titled "Update of the clinical competence statement on coronary artery interventional procedures" states recommended thresholds of ≥200 procedures per year at an institution with operators with experience of ≥50 procedures per year (averaged over a 2-year period).[1099] Old studies reported that more procedures performed would improve in-hospital outcomes, but more recent studies no longer suggest such a simple association.[1100–1102]

In Japan, an analysis of 323,322 procedures performed by 4,211 operators at 625 institutions was performed using the J-PCI data (years 2014 and 2015) of the National Clinical Database and published in 2017.[1103] The number of institutions that perform PCI in Japan is large compared with its small geographic area, making the number of procedures performed per institution smaller compared with Europe or the USA. According to the report, only about half of the institutions that perform PCI in Japan met the annual threshold of ≥200 procedures stated in the ACCF/AHA/SCAI guideline.

The report also revealed that the number of procedures was related to in-hospital mortality rate and the incidence of complications. At institutions with <150 procedures per year, both the incidence of in-hospital mortality and complications were significantly higher than at institutions with ≥150 procedure per year. In addition, the Japanese study indicated that the in-hospital mortality rate and the incidence of complications tend to even out as the number of procedures performed at an institution per year exceeds around 100, suggesting that a different volume–outcome relationship pattern may exist in Japan. The report also noted no correlation was found between the number of procedures performed by operators and the outcomes of PCI.

2. CABG

The volume–outcome relationship of CABG was initially assessed using raw data without adjustment by preoperative risk. According to an analysis published in 2007 based on survey data of the JATS, the 30-day mortality rate for CABG patients was 3.4% at institutions with ≤24 procedures per year ("low-volume institutions") compared with 1.3% at institutions with ≥100 procedures ("high-volume institutions") with an odds ratio of 2.40 for the small-volume institutions.[1104] This is a significant figure at first glance. However, because of the large variability in reported outcomes at low-volume institutions, the report suggested the data might not be accurate. In 2012, the same analysis was performed using data from 2005 to 2009 and reported a 30-day mortality rate of 2.72% for low-volume institutions and 1.00% for high-volume institutions (odds ratio, 2.52).[1105] The more recent report revealed better outcomes of CABG in general, but still indicated a volume–outcome relationship. Large variability in low-volume institutions still existed in the recent reports.

The JCVSD is the first database that allowed the use of data adjusted for risk for analysis of the volume–outcome relationship in CABG patients in Japan.[162] In the report published in 2008, the 30-day operative mortality rate was 4.1% for institutions with 16–30 CABG procedures per year (institutions with ≤15 procedures were excluded because of their variability), 2.8% for institutions with 31–50 procedures per year, and 1.6% for institutions with ≥51 procedures per year.[1106] The JCVSD allows isolation of data by individual operators. Just as with PCI, the report indicated no correlation between the number of procedures performed by an operator and the outcome of CABG, suggesting the outcomes of CABG depend much on the institution as a whole rather than individual operator skill.

The risk-adjusted mortality rate, calculated using the number of CABG performed at each institution and by each operator, was 2.05% for expert operators with ≥16 procedures per year at institutions with 16–30 procedures per year compared with 1.70% for non-expert operators with ≤15 procedures per year at institutions with ≥51 procedures per year. Operators who perform only a relatively small number of CABG per year at high-volume institutions therefore can and do attain similar outcomes of CABG to those by operators who perform a relatively large number of CABG per year at low-volume institutions, implying the importance of the number of procedures performed at institutions where training on the CABG procedure takes place. Variability in outcomes noted at small-volume institutions was less conspicuous at institutions with ≥40 procedures a year, suggesting 40 procedures/year may be used as a threshold for more consistent outcomes.[1106]

XI. Health Economics

1. Cost-Effectiveness Measures

Rising healthcare expenses, partly due to the aging of the population and advances in healthcare technologies, are increasing pressure on Japan's National Healthcare Insurance system. Accurate assessment of the value and efficiency of care is required to keep medical expenses in check.

The quality-adjusted life year (QALY) is a measure commonly used in health economics. A QALY combines survival and QOL into a single index. A QALY of 1 translates into 1 year of survival with perfect health. The efficiency of medical care is often assessed using cost–benefit analysis. The incremental cost-effectiveness ratio (ICER) is used to calculate the economic value of an intervention compared with an alternative. When the ICER of an intervention is smaller than a certain reference value, the intervention is regarded as cost-efficient. There is no internationally-agreed cost-per-QALY threshold for ICER. In the USA, however, $50,000 is often used.

In the era of rapid drug development and advances in PCI techniques combined with continuous fluctuation in drug/medical device prices, the old cost–benefit analyses cannot be applied to today's medical care. Because of differences in healthcare systems among countries, a cost–utility analysis of a treatment in a foreign country is normally not applicable in Japan. Most studies of the cost-effectiveness of coronary artery revascularization are reported from outside Japan. Data included in such studies are discussed in subsequent paragraphs. Japanese researchers recently proposed a QALY calculation model using utility indices recorded before and after PCI.[1107] More evidence is needed for comparison of the cost-effectiveness of treatments given to Japanese patients with stable CAD.

2. PCI vs. Medical Therapy

The COURAGE study reported that adding PCI to OMT in stable CAD patients did not improve survival, while increasing the cost of PCI ($10,000), and the lifetime ICER of PCI was $168,019 dollars per QALY gained.[88,1108] However, PCI was not ischemia-guided and used only dated techniques in the study.

In the FAME 2 study of stable CAD patients, FFR-guided PCI performed with 2nd-generation DES decreased cardiovascular events (particularly the need for urgent revascularization) compared with medical therapy alone. The decrease was subsequently reconfirmed after a 3-year follow-up.[40,41,134] The study reported a higher average cost initially for PCI ($9,944 for PCI and $4,440 for medical therapy alone; P<0.001). After 3 years, however, cost was similar between the 2 groups (respectively $16,792 and $16,737; P=0.94).[41] With respect to cost-effectiveness, the ICER for FFR-guided PCI compared with medical therapy alone was $17,300 per QALY at 2 years and $1,600 per QALY at 3 years, both below the threshold of $50,000 commonly used in the USA. FFR-guided PCI is likely to improve long-term outcomes and also be a cost-effective treatment strategy compared with medical therapy alone.

3. BMS vs. DES

Although BMS are no longer used frequently in PCI, a meta-analysis of RCT data has reported a cost-effectiveness comparison between the cobalt-chromium EES (CoCr-EES) and BMS.[1109] According to the analysis, CoCr-EES prolonged QALY per patient by 0.018 compared with BMS, saved $236, and was cost-effective (ICER ≤$50,000) at a probability of ≥99% compared with BMS.

An analysis of data from the SPIRIT IV study reported a comparison between 1st- and 2nd-generation DES.[1110] The 2nd-generation EES significantly decreased target lesion failure compared with the PES,[1111,1112] and saved $273 dollars per patient vs. PES over 2 years.[1110] The ICER of PCI with EES was ≤$50,000 at a probability of 85.7%. Newer-generation (i.e., 2nd-generation and later) DES likely have better clinical outcomes and are more cost-effective than BMS and 1st-generation DES.

4. PCI vs. CABG (vs. Medical Therapy)

The well-known SYNTAX study compared PCI using DES with CABG and revealed the superiority of CABG to PCI with the PES in LMCA disease or 3-vessel disease.[142,1113] The study also reported that CABG saved $3,415 of the initial procedural cost but required $10,036 more for hospital stay compared with PCI.[1114] Over the subsequent 5-year follow-up, PCI was more costly due to more frequent hospitalization, revascularization procedural cost, and higher medication cost. Over a lifetime horizon, CABG was more costly than PCI, but the ICER of CABG vs. PCI in the study was favorable: $16,537 per QALY gained. However, PCI was more cost-efficient in patients with LMCA disease or a SYNTAX score ≤22 or those for whom SYNTAX score II favored PCI based on lower predicted 4-year mortality rate with PCI vs. CABG.[1114,1115]

The FREEDOM study in patients with DM and multivessel disease compared PCI (mostly with 1st-generation DES) on top of aggressive medical therapy vs. CABG, and reported a significantly lower incidence of events for CABG over a median follow-up of 3.8 years.[172] As in the SYNTAX study, initial procedural cost was lower for CABG, but the total cost through the index hospitalization was higher for CABG by $8,622.[1116] Over the subsequent 5 years, PCI was more costly due to more frequent repeat revascularization and higher outpatient medication costs. Nevertheless, the cumulative expense, including the initial costs, were higher for CABG by $3,641. The cumulative 5-year QALY was 0.0312 longer for CABG. The ICER for CABG was $8,132 per QALY gained and estimated to fall below $50,000 per QALY at a probability of 99.2%.

The MASS II study compared medical therapy, PCI (POBA alone or with stent placement), and CABG in multivessel disease patients with preserved left ventricular function (mean ejection fraction 67%). Events were more frequently reported for medical therapy and PCI than for CABG over the 5- and 10-year follow-up periods.[495,1117,1118] The study estimated the event-free cost over 5 years was $9,071 dollars for medical therapy, $19,967 for PCI, and

$18,263 for CABG, and noted that medical therapy was most cost-effective, followed by CABG.[1119]

The ASCERT study was a large observational study and compared the long-term (≥4 years) effectiveness of PCI and CABG in multivessel disease patients with stable CAD.[1120] The ACC and STS databases were linked to the centers for Medicare and Medical Services claims data to compare cost-effectiveness between CABG (86,244 patients) and PCI (103,549 patients). The costs by propensity score bin bootstrapping were higher for CABG for the index hospitalization ($24,290 for CABG and $13,620 for PCI), for the observation period from 2004 to 2008 ($63,785 vs. $55,640), and for the lifetime ($184,933 vs. $173,358). However, patients undergoing CABG gained an average of 0.2525 longer QALYs over the observation period and 0.3801 lifetime QALYs relative to PCI. The lifetime ICER of CABG vs. PCI was $30,454 per QALY gained.

Although a number of studies have reported the superior cost-effectiveness of CABG vs. PCI, most patients in these studies did not undergo PCI using newer-generation DES. More data and domestic studies are therefore needed for an accurate and current cost–utility assessment of PCI.

XII. AUC and Standardized PCI

1. AUC

Recommendations presented in guidelines based primarily on data from large RCTs have long been considered to form the foundation of evidence-based medicine. However, because recommendations in clinical practice guidelines are estimated to cover merely 20–30% of patients, the limitations of their applicability have been noted. Hence, AUC (described in **Section 3.1** "**Input Into Treatment Planning**" page 492 of **Chapter IV**) were developed to give better guidance on appropriate use of tests and procedures.

The AUC presents recommendations for more individualized scenarios for which consensus is established by a modified Delphi method using relevant questions (e.g., location of disease, presence/absence of ischemia, and medications administered). Since the publication of the COURAGE study, AUC have been gaining interest as a practical tool for suitability assessment of revascularization strategies. It is now commonly used by healthcare teams to reflect on the decisions they make in daily clinical practice.[1121]

In the USA, the first version of AUC for revascularization was published in 2009, followed by the first revision in 2012, and another in 2017.[170,1122–1124] Analysis of revascularization registry data show that most emergency PCI procedures are performed in accordance with the AUC: 10% of elective PCI was deemed "inappropriate." When the revised AUC (2012 version) was applied, the percentage of "inappropriate" elective PCI become more than 25%.[1125,1126]

A similar estimate has been reported for elective PCI in Japan. The reported percentage of inappropriate PCI was 15%, according to the AUC of 2009, and 30% according to the criteria of 2012. Coronary CT angiography was commonly performed in Japan, and this modality was considered appropriate as a preoperative test in the AUC. Therefore, the older versions of the AUC could not be directly applied to some of the cases in Japan.[1127,1128] The updated US AUC published in 2017 includes scenarios in which coronary CT or FFR is used for guidance and is generally congruous with their clinical practice pattern.

There were also differences when considering the appropriateness in applying revascularization for patients who do not have proximal LAD disease and with low ischemic risk.[1129] The US AUC recommend medical therapy in such patients. In Japan, both medical therapy and PCI are established as first-line, mostly based on the results of the J-SAP study.[1130,1131] This may be one of the reasons why PCI is more frequently performed in lower-risk patients in Japan.

The spread of AUC has cut the ratio of "inappropriate" PCI by 50% and decreased elective PCI by 30% in the USA.[1132] However, even the current US AUC cannot be applied directly in Japan. Nevertheless, unnecessary or inappropriate PCI does take place in Japan as elsewhere. Medical institutions and the healthcare industry should continue to improve efforts eliminate unnecessary/inappropriate PCI.

2. Standardized PCI (Table 69)

Despite the substantial clinical benefit, of PCI, the skill of the person who performs the procedure often affects its outcome. PCI operators are expected to acquire and maintain their skillset, and should ideally perform a sufficient number of procedures for its maintenance. The Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT) specifies the minimum number of PCI performed as primary operator for qualification as a "Fellow" or "Board-Certified Member."

As for considering the appropriate indication for PCI, the Japanese medical service fee revision report of the fiscal year 2018 stated that new criteria to evaluate the necessity for each medical care/service given will be introduced in a reimbursement review. For elective PCI, ischemic dysfunction confirmed by preoperative testing is specified as the requirement for reimbursement from the NHI program.[1133] This new requirement is a call for more appropriate use of medical procedures.

In a move to respond to this new social demand, the

Table 69. Recommendation and Evidence for Standardized PCI

	COR	LOE
Control quality and outcomes of PCI and CABG by referencing nationwide data	I	C
Member societies of the JCS Joint Working Group establish their own databases and engage in quality control	I	C
Share data with other institutions	I	C

CABG, coronary artery bypass grafting; COR, class of recommendation; JCS, Japanese Circulation Society; LOE, level of evidence; PCI, percutaneous coronary intervention.

Table 70. 7 Performance Indices of "Standardized PCI" Initiative

1. Percentage of patients with acute coronary syndrome (Item 11)
2. Percentage of emergency PCI (Item 19)
3. Percentage of patients with preoperative antiplatelet therapy (Item 13–3)
4. Percentage of patients who undergo ischemia assessment before non-emergency PCI (Item 13–1)
5. Door-to-balloon time in patients with ST-segment elevation acute myocardial infarction (Item 19–1)
6. Percentage of radial artery access (Item 121)
7. Percentage of non-emergency PCI in non-main coronary artery (other than segments 1–3, 5–7, and 11) (Item 24 and later)

PCI, percutaneous coronary intervention. "Item" numbers correspond to those on the J-PCI registry. (From Nakao K, 2018.[1134])

CVIT has launched their "Standardized PCI" initiative. The CVIT requires each of their member training facilities or other associated training facilities to register all PCI to the national J-PCI registry. The registration system allows simple comparison of institutional case data with data from other institutions across the country. The CVIT registry steering committee has defined 7 performance indices, shown in **Table 70** (feedback system of the CVIT's J-PCI registry),[1134] per institution to allow individual institutions to put their practice into perspective. Because only a small number of variables are included, the J-PCI registry, unlike the US AUC, is not expected to have an immediate effect on whom PCI is performed. However, it will visualize each institution's attitude towards advance ischemia assessment and intervention in side branches and provide an opportunity to reflect on their practice of PCI against national averages.

This CVIT's work with the "Standardized PCI" initiative has just started. It is a meaningful response to society's call for more appropriate use of healthcare resources.

XIII. Future Outlook

1. Robot-Assisted PCI

1.1 Outline and Rocedure

A robot-assisted PCI system was approved in 2018 in Japan. The system comprises a bedside subunit and remote interventional cockpit.

The operator sits in front of the remote interventional cockpit, installed away from the angiography table and surrounded by a radiation shield. The operator manipulates the guidewire, and balloon catheter/stent, and engages the guidewire using separate controls while looking at the fluoroscopy and recording monitors in the cockpit. The bedside unit inserts the guidewire, selects the target vessel, inserts and positions the balloon, and places the stent as instructed by the operator in the cockpit. Although the bedside unit is capable of performing many of the tasks normally performed by a human operator, insertion of the sheath, guiding catheter insertion and positioning, and attachment of balloon/stent to the guiding catheter must be done manually. A 6–7F guiding catheter can be used with the system. The system allows intervention in a main coronary artery while protecting its side branch with a guidewire. The system does not need special guidewire, balloons, or stents and is capable of handling both radial and femoral artery access.

1.2 Indications, Benefits, and Limitations

When the first robotic PCI system was released, it was recommended for only single-stenting in a lesion not longer than 24 mm.[1135] Today's systems are capable of handling complex disease (AHA classification type B2/C).[1136,1137] For CTO lesions, manual PCI up to guidewire insertion to the lesion is combined with robotic PCI for balloon dilatation through to stent placement.

This can somewhat prolong the duration of the procedure due to the time needed for setup of the system, but it reportedly does not change the fluoroscopy time.

Robotic PCI has significantly less stent placement error in the longitudinal direction compared with manual PCI,[1138] which may allow reduction of contrast media. The greatest benefit of robotic PCI is ≥90% reduction of the primary operator's exposure to radiation compared with manual PCI. Health issues associated with radiation exposure among healthcare professionals are widely acknowledged and are a concern raised among hospital management. Robotic systems are also considered to have the potential for application in long-distance PCI. Current limitations of robotic systems include phased-array IVUS being the only intravascular imaging modality compatible with the systems.

2. Hybrid Coronary Revascularization (HCR)

2.1 Overview

HCR combines CABG and PCI into 1 operation in multivessel disease. A common definition of HCR includes (1) minimally invasive direct coronary artery bypass (MIDCAB; may include the use of a robotic system) in a LITA-to-LAD grafting, (2) PCI using DES, and (3) either 1-stop or staged (≤60 days) procedure.[1139]

CABG with LITA has favorable long-term outcomes and is a standard treatment in patients with severe multivessel disease. When SVGs are used, CABG is unable to achieve a satisfactory long-term patency rate. Stents placed in PCI now have a better long-term patency rate than SVG thanks to the reduction in both ST and ISR over the years (**Figure 9**).[1140]

HCR aims to combine the favorable long-term outcomes of CABG with the benefit of less invasive PCI while simultaneously reducing the shortcomings of each technique. HCR is estimated to account for 0.5% of all CABG performed in the USA.[1141]

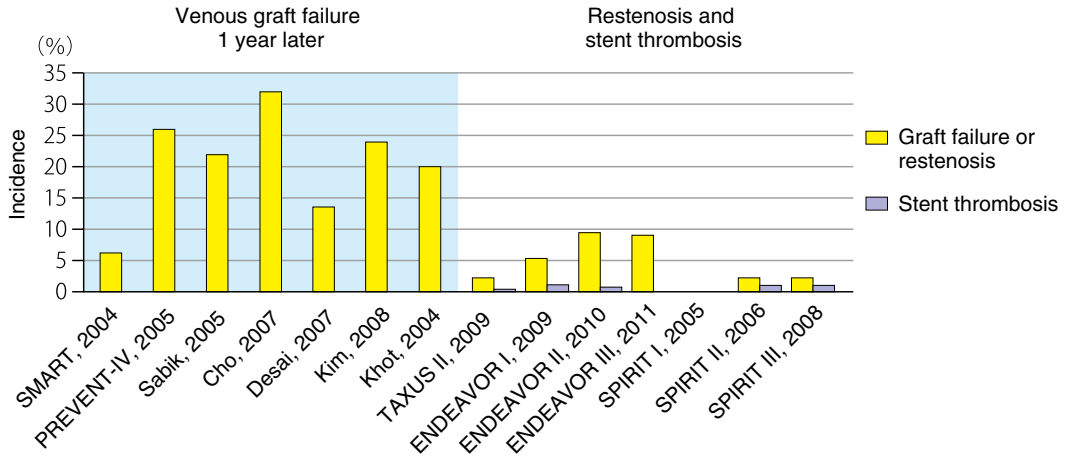


Figure 9. Revascularization failure rates with venous grafts and drug-eluting stents. (From Harskamp RE, et al. 2013.[1139] Copyright (2013) by the Society of Thoracic Surgeons, with permission from Elsevier. https://www.annalsthoracicsurgery.org/)

2.2 Indications

Determining whether HCR is feasible and safe (**Table 71**) requires knowledge of the latest evidence on PCI and CABG. As discussed earlier in this guideline, most of the reliable evidence comes from RCTs comparing DES vs. CABG, including the SYNTAX study,[142] FREEDOM study,[172] EXCEL study,[193] NOBLE study,[194] a pooled analysis of data from 11 RCTs,[173] and the ASCERT study that analyzed data from databases across the USA.[1142,1143]

The ACC/AHA guideline published in 2012 states that HCR is indicated for (1) patients who are not amenable to CABG because of severe calcification in the ascending aorta or narrow target lesions, (2) patients with a lack of suitable graft conduits, or (3) when PCI of the LAD artery is not feasible because of excessive tortuosity or CTO (Class IIa).[181] HCR should also be considered in older patients, patients with severe comorbidities, and patients with a history of cardiotomy or thoracic radiation therapy.[1144,1145]

Alternatively, CABG is indicated for patients who are not suitable for DAPT, patients with valve disease requiring surgery, patients with poor vascular access, and patients who have non-LAD complex disease not amenable to PCI. PCI is indicated for patients with severe obstructive lung disease and patients who do not have suitable ITA graft conduits.[1146,1147]

Table 71. Patient Selection Criteria for Hybrid Coronary Revascularization

Indicated
- Not amenable to CABG (severely calcified ascending aorta, aortic valve, or mitral valve)
- Lack of suitable non-ITA graft conduits
- LAD disease not amenable to PCI (total occlusion, severe calcification, bifurcation lesion) but its distal side allows bypass grafting
- Non-LAD lesion amenable to PCI
- History of CABG
- History of thoracic radiation therapy
- Residual lesion in LAD or otherwise after PCI for acute coronary syndrome
Contraindicated
Patient-related factors
- Not suitable for DAPT
- History of severe obstructive lung disease or left thoracotomy
- Valve disease requiring surgery
- Unstable angina
Anatomic risk factors
- Non-LAD complex disease
- No suitable ITA for graft conduits

CABG, coronary artery bypass grafting; DAPT, dual antiplatelet treatment; ITA, internal thoracic artery; LAD, left anterior descending coronary artery; PCI, percutaneous coronary intervention.

2.3 One-Stop or Staged

A recently reported meta-analysis noted little differences in the outcomes of 1-stop and staged HCR (in-hospital mortality, perioperative myocardial infarction/ cerebral infarction/ repeat revascularization, 1-year survival).[1148] A standard HCR procedure is carried out with a small, left anterior thoracotomy incision and without heart–lung machine.

The 1-stop HCR typically starts with MIDCAB in the hybrid operating room, followed by PCI. Close coordination between the surgeon and cardiologist is required for successful HCR. For staged HCR, CABG is normally completed first. In patients with a severe non-LAD lesion, PCI must follow soon after CABG. PCI prior to CABG is effective in non-LAD culprit lesions in patients with ACS. In this instance, the use of DES in PCI performed before CABG in HCR is controversial.[1149,1150]

2.4 Outcomes and Limitations

Most reports on the outcomes of HCR give short-term results and come from single-center studies. HCR reportedly has a similar 30-day mortality rate, 1-year survival

rate, and incidence of MACCE, but less frequent perioperative complications (rethoracotomy, renal failure, mechanical ventilation time), less blood transfusion, and shorter hospital and ICU stay compared with CABG.[1151,1152] QOL was maintained better with HCR vs. CABG 6 weeks after discharge.[1148] Meta-analyses generally show a similar incidence of MACCE between HCR and CABG, but tend to report a higher rate of repeat revascularization for HCR.[1148,1151,1153] The only RCT between HCR and CABG has reported similar 5-year clinical outcomes.[1154,1155] A multicenter study reported a similar incidence of MACCE over 1 year between HCR and PCI in multivessel disease.[1156] However, evidence is generally lacking on comparisons between HCR and PCI. The recent popularity of FFR guidance in PCI increases the importance of current data in order to make a more relevant comparison between the procedures.

The reported rates of ISR and thrombosis after HCR are 9–13% and 2.2–3.7%, respectively.[1157–1159] In patients who undergo PCI first, discontinuation of DAPT for CABG is thought to increase ST, but the estimated incidence of ST was equivalent to 3.3% at 1 year in the SYNTAX study.[1113]

In general, HCR is a safe procedure when performed in carefully selected patients. Medium-term outcomes of HCR are similar to those of CABG. Because PCI and CABG are individually established therapies for CAD, however, HCR needs to demonstrate its superiority over PCI or CABG. Bilateral ITA (BITA) grafts commonly used in CABG in Japan only show their superiority over single ITA after around 10 years. This means a longer follow-up is necessary for a comparison, and HCR using BITA is potentially a suitable option.

3. Minimally Invasive CABG (Table 72)

3.1 Definition and Benefits

Minimally invasive CABG is generally defined as off-pump multivessel bypass grafting with a small left intercostal incision instead of median sternotomy. Single-vessel bypass grafting of the LITA to the LAD is called MIDCAB.[1160]

Minimally invasive CABG is typically used in multivessel bypass grafting in addition to LITA-to-LAD anastomosis. Its potential benefits compared with CABG include less blood loss and blood transfusion, reduction of AF, less use of inotropes, lower risk of respiratory infections, early extubation, early discharge from the ICU, and shorter hospital stay. Avoiding median sternotomy can eliminate the risk of mediastinitis and less blood loss/transfusion. MIDCAB in patients with chronic obstructive pulmonary disease is reported to decrease postoperative complications.[1161]

Table 72. Recommendation and Evidence for Minimally Invasive CABG

	COR	LOE
Minimally invasive CABG is associated with less frequent onset of mediastinitis and requires less blood transfusion compared with ONCAB	IIb	C

CABG, coronary artery bypass grafting; COR, class of recommendation; LOE, level of evidence; ONCAB, on-pump coronary artery bypass.

Minimally invasive CABG shares the following limitations/shortcomings with OPCAB with median sternotomy compared with traditional CABG: a smaller number of bypasses and doubtful long-term outcomes because anastomoses constructed on a beating heart in general have an increased risk of graft stenosis/occlusion.[1162–1165] Because of the general difficulty of bypass grafting to the RCA, HCR is also performed.[1147,1166–1168]

To some, minimally invasive CABG is multivessel bypass grafting through a small left intercostal incision (i.e., rather than median sternotomy) with cardiopulmonary bypass, but this procedure may become more invasive. A study noted that, even if about 20% of patients use cardiopulmonary bypass in minimally invasive CABG, the procedure still has the benefit of early return to normal life and avoidance of mediastinitis.[1164]

Cardiac surgeons with no or limited experience in OPCAB will be able to start minimally invasive CABG with cardiopulmonary bypass or HCR without complications. Regardless of cardiopulmonary bypass, side-clamping of the ascending aorta has been shown to increase the risk of atherothrombotic stroke.[1169] To avoid atherothrombotic stroke, in situ graft and composite graft for distal anastomosis is necessary when the ascending aorta is atherosclerotic.

3.2 Totally Endoscopic Coronary Artery Bypass (TECAB), Awake OPCAB

TECAB is the least invasive type of CABG. TECAB uses the robotic da Vinci Surgical System[1170,1171] and requires special anastomotic devices when cardiopulmonary bypass is not used. TECAB can be made easier when cardiopulmonary bypass is used, but this inevitably makes the procedure more invasive.

Awake OPCAB is performed with a median sternotomy while the patient is awake and having spontaneous breathing under thoracic epidural anesthesia.[1172,1173] Patients who undergo awake OPCAB can achieve early mobilization and discharge by avoiding intubation and general anesthesia. Decreased heart rate increases coronary blood flow during the procedure, which is claimed to reduce arrhythmia and help make anastomosis easier.

4. Cardiac Regeneration

Heart transplantation is the most important treatment option for patients with severe HF, but heart donors are constantly in short supply. The amendment of the Organ Transplant Law in 2009 is unlikely to succeed in making heart transplant as nearly accessible as in Europe or the USA. Left ventricular assist device (LVAD) is another treatment option for severe HF patients. In Japan, outcomes of LVAD therapy given as a bridge to heart transplant are troubled by complications such as infections and cerebral thrombosis due to the long waiting period for a heart transplant. Although expectations for regenerative medicine are high around the world, available treatments are not yet capable of curing severe HF. We need new treatments that can support/enhance the effectiveness of existing treatments for severe HF such as heart transplant and LVAD.

Research is ongoing for clinical application of new cell/tissue transplant methods as well as regenerative treatments.

4.1 Overview of Autologous Myoblast Sheet

Myoblast sheet transplant is a cellular therapy for severe HF. The patient undergoes left thoracotomy and has 5 sheets of 6×10^7 myoblast cells each (**Figure 10**) transplanted onto a large area of the heart from the left ventricular anterior to lateral walls. For this treatment, skeletal muscle of about 5–10 g is isolated from the femoral vastus medialis, cultured, and frozen. The culture cells are thawed when the date of transplantation is fixed. The cells are formed into sheets on temperature-responsive culture dishes for transplantation.

Implanted cells fall under ischemic and are expected to express the HIF-1 gene, which should then induce secretion of cytokines such as hepatocyte growth factor, vascular endothelial growth factor, basic fibroblast growth factor, and stroma cell-derived factor 1 (SDF-1) that help achieve cardiac regeneration through their promotion of angiogenesis, and stem cell induction, and inhibition of fibrosis. Preclinical research has shown that, although the myoblast sheets disappear after a few months, angiogenesis occurs within 1 month. Also, bone marrow mesenchymal stem cells induced in the area by SDF-1 further promote angiogenesis and some of them form part of new vessels.[1174]

A cell processing room is required for the culture of myoblast cells in a clean environment. This precludes patients infected by viruses such as HIV or hepatitis from myoblast sheet transplantation. Studies in HF animal models have shown myoblast sheet transplantation improves cardiac function and survival.

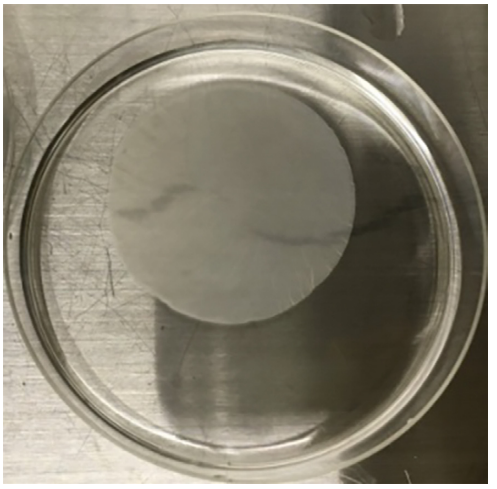


Figure 10. Autologous myoblast sheet for cardiac regeneration.

4.2 Efficacy of Myoblast Sheet

Autologous myoblast sheets have been implanted in 4 dilated cardiomyopathy patients with LVAD. Improved cardiac function was observed in 2 patients who subsequently had the LVAD removed.[1175] In ischemic cardiomyopathy patients, a clinical trial[1176] and sponsored multicenter trial[1177] have demonstrated the safety and efficacy of myoblast sheet transplantation. The myoblast sheet product "HeartSheet" has been designated under Japan's accelerated approval program and listed in the National Health Insurance list as the world's first regenerative medical product for the treatment of HF. Regulatory approval is expected when efficacy is demonstrated in 60 ischemic cardiomyopathy patients against control.

In a single-arm study, myoblast sheet transplantation in ischemic cardiomyopathy patients improved cardiac function, alleviated HF symptoms, and significantly decreased B-type natriuretic peptide, pulmonary arterial pressure, and pulmonary artery pressure.[1176] A physician-initiated trial conducted in children and adults with dilated cardiomyopathy to widen the potential indications of the product has been completed. Whether the product is suitable for a wider patient population is being evaluated.

The efficacy of myoblast sheets has been demonstrated only in a small number of patients with severe HF. The profile of patients who will respond to the treatment needs to be established.

The Regenerative Medicine Subcommittee under the Health Sciences Council of Japan recently approved the conducting of the first-in-human clinical trial of transplantation of iPS-derived myocardial cells that are presumed to be more effective than myoblast cells.[1178]

End Note

Who is the target audience of the guidelines? No guidelines have or are intended to have a legally binding effect. As with any other guidelines, this guideline only presents the treatments established and accepted as standard practice based on evidence. This guideline is written on the assumption that individual institutions can perform coronary artery revascularization with a standard quality. Achieving and maintaining high standards of care requires technical skills of both cardiologists and cardiovascular surgeons. The Heart Team is expected to play the central role in treatment decision-making. Sharing of clinical outcomes of treatments administered within an institution is essential for the effectiveness of the team.

Individual institutions may choose treatments with Class IIb or III recommendation over one with Class I recommendation. It is entirely acceptable depending on the circumstances. However, the Heart Team is expected to discuss and reach consensus when making such a decision. The patient must of course be presented with the reason for the treatment the Team has chosen. Finally, we consider that the academic societies involved in publication of this guideline are responsible for gathering data regarding the level of adherence to the recommendations presented here, in the clinical setting as well as the clinical outcomes of treatments administered according to the recommendations.

Some recent medical malpractice lawsuits were filed claiming that doctors failed to provide adequate information to the patients as suggested in clinical practice guidelines. There are also cases filed against the academic societies publishing the guidelines on the grounds that they failed to

carry out supervisory obligations. An article published in 2002 titled "Medical Professionalism in the New Millennium: A Physician Charter" stated that striving for evidence-based medicine is the doctor's obligation.[1179] Acting professionally will become more important for doctors and will protect themselves from lawsuits and also protect the patients from unnecessary/inappropriate treatments.

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Appendix 1. Japan's Regulatory Requirements for Facilities Where PCI Is Performed

The current requirements for an institution to perform percutaneous coronary intervention (PCI) are having at least 1 full-time cardiovascular surgeon with at least 5 years of experience in employment and posting of a cardiovascular surgery department. An institution that has a working patient referral program with another institution that meets this requirement is also regarded as a qualified institution. Registration of the institution with the head of the local bureau of health and welfare is no longer required.

The use of the high-speed rotational percutaneous atherectomy catheter (Rotablator®) requires registration with the local bureau of health and welfare.

HI/ME Notification No. 0305-3, March 5, 2018

Item 62-3 Percutaneous Transluminal Coronary Angioplasty

1. Institutional Requirements for Percutaneous Transluminal Coronary Angioplasty
   The number of percutaneous transluminal coronary angioplasties performed the previous year (from January through December) must be displayed by the following categories:
   (1) For the treatment of acute myocardial infarction
   (2) For the treatment of unstable angina
   (3) For the treatment of other diseases/conditions
2. Registration
   Registration with the head of local bureau of health and welfare is unnecessary for an institution to perform Percutaneous Transluminal Coronary Angioplasty.

Item 63-2 Percutaneous Coronary Artery Stenting

1. Institutional Requirements for Percutaneous Coronary Artery Stenting
   The number of percutaneous transluminal coronary angioplasties performed the previous year (from January through December) must be displayed under the following categories:
   (1) For the treatment of acute myocardial infarction
   (2) For the treatment of unstable angina
   (3) For the treatment of other diseases/conditions
2. Registration
   Registration with the head of the local bureau of health and welfare is unnecessary for an institution to perform Percutaneous Coronary Artery Stenting.

HI/ME Notification 0305-3, March 5, 2010

Item 63 Percutaneous Transluminal Coronary Angioplasty (with the Use of High-speed Rotational Percutaneous Atherectomy Catheter)

1. Institutional Requirements for Percutaneous Transluminal Coronary Angioplasty (With the Use of High-speed Rotational Percutaneous Atherectomy Catheter)
   (1) Institution with signs of cardiology and cardiovascular surgery departments posted.

(2) Cardiotomy or coronary artery (or aortic) bypass performed in at least 30 patients per year and Percutaneous Transluminal Coronary Angioplasty performed in at least 200 patients per year.
(3) At least 1 doctor with ≥5 years of experience in cardiology and at least 1 full-time doctor with ≥5 years of experience in cardiovascular surgery are employed.

2. Registration
An institution that plans to perform Percutaneous Transluminal Coronary Angioplasty (With the Use of High-speed Rotational Percutaneous Atherectomy Catheter) must submit Forms 52 and 59 included in Annex 2 for prior registration.

Appendix 2. Details of Members

Chairs
- Masato Nakamura, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center
- Hitoshi Yaku, Department of Cardiovascular Surgery, Kyoto Prefectural University of Medicine

Members
- Junya Ako, Department of Cardiovascular Medicine, Kitasato University Graduate School of Medical Sciences
- Hirokuni Arai, Department of Cardiovascular Surgery, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University
- Tohru Asai, Department of Cardiovascular Surgery, Juntendo University Graduate School of Medicine
- Taishiro Chikamori, Department of Cardiovascular Medicine, Tokyo Medical University
- Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine
- Kiyoshi Doi, General and Cardiothoracic Surgery, Gifu University Graduate School of Medicine
- Toshihiro Fukui, Department of Cardiovascular Surgery, Graduate School of Medical Sciences, Kumamoto University
- Toshiaki Ito, Department of Cardiovascular Surgery, Japanese Red Cross Nagoya Daiichi Hospital
- Kazushige Kadota, Department of Cardiology, Kurashiki Central Hospital
- Junjiro Kobayashi, Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center
- Tatsuhiko Komiya, Department of Cardiovascular Surgery, Kurashiki Central Hospital
- Ken Kozuma, Department of Internal Medicine, Teikyo University Faculty of Medicine
- Yoshihisa Nakagawa, Department of Cardiovascular Medicine, Shiga University of Medical Science
- Koichi Nakao, Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center
- Hiroshi Niinami, Department of Cardiovascular Surgery, Tokyo Women's Medical University
- Takayuki Ohno, Department of Cardiovascular Surgery, Mitsui Memorial Hospital
- Yukio Ozaki, Department of Cardiology, Fujita Health University Hospital
- Masataka Sata, Department of Cardiovascular Medicine, Tokushima University Graduate School of Biomedical Sciences
- Shuichiro Takanashi, Department of Cardiovascular Surgery, Kawasaki Heart Center
- Hirofumi Takemura, Department of Cardiovascular Surgery, Graduate School of Medical Sciences, Kanazawa University
- Takafumi Ueno, Devision of Cardiology, Fukuoka Kinen Hospital
- Satoshi Yasuda, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center
- Hitoshi Yokoyama, Department of Cardiovascular Surgery, Fukushima Medical University

Collaborators
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- Shun Kohsaka, Department of Cardiology, Keio University School of Medicine
- Takashi Kubo, Department of Cardiovascular Medicine, Wakayama Medical University
- Susumu Manabe, Department of Cardiovascular Surgery, Tsuchiura Kyodo General Hospital
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- Noboru Motomura, Department of Cardiovascular Surgery, Graduate School of Medicine, Toho University
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- Hiromasa Otake, Department of Cardiovascular Medicine, Kobe University Graduate School of Medicine
- Fumiyuki Otsuka, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center
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- Kazunori Shimada, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine
- Tomoki Shimokawa, Department of Cardiovascular Surgery, Sakakibara Heart Institute; Department of Cardiovascular Surgery, Teikyo University Faculty of Medicine
- Toshiro Shinke, Division of Cardiology, Department of Medicine, Showa University School of Medicine
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- Masao Takahashi, Department of Cardiovascular Surgery, Hiratsuka Kyosai Hospital
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- Kazuo Kimura, Cardiovascular Center, Yokohama City University Medical Center
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- Yoshitaka Okamura, Department of Cardiovascular Surgery, Seiyu Memorial Hospital
- Minoru Ono, Department of Cardiac Surgery, Graduate School of Medicine, The University of Tokyo
- Hiroki Shiomi, Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University
- Kazuo Tanemoto, Department of Cardiovascular Surgery, Kawasaki Medical School

(Listed in alphabetical order; affiliations as of March 2019)

Appendix 3. Disclosure of Potential Conflicts of Interest (COI): JCS/JSCVS 2018 Guideline on Revascularization of Stable Coronary Artery Disease (2016/01/01–2018/12/31)

Name	Personal									Spouse, 1st-degree family member, or any other person with whom the person shares income/asset			Principal/employer (when the person is a member of the research team headed by the principal/employer)	
	Consultancy	Equity	Patent royalty	Speaking fee	Manuscript fee	Research grant	Scholarship fund	Endowment course	Other	Consultancy	Stock	Patent	Research grant	Scholarship fund
Chair: Masato Nakamura				Sanofi K.K. TERUMO CORPORATION Daiichi Sankyo Company, Limited	Daiichi Sankyo Company, Limited	Sanofi K.K. Daiichi Sankyo Company, Limited								
Chair: Hitoshi Yaku				Medtronic Japan Co., Ltd. Abbott Medical Japan L.L.C										
Member: Junya Ako				MSD K.K. Astellas Pharma Inc. Amgen Astellas BioPharma K.K. Astellas Pharma Inc. AstraZeneca K.K. ABBOTT JAPAN CO., LTD. Abbott Vascular Japan Co., Ltd. Eli Lilly Japan K.K. Sanofi K.K. TERUMO CORPORATION Bayer Yakuhin, Ltd. Bristol-Myers Squibb Kowa Pharmaceutical Co., Ltd. Ono Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited			Astellas Pharma Inc. Abbott Vascular Japan Co., Ltd. Nipro Corporation Bayer Yakuhin, Ltd. Pfizer Japan Inc. Kowa Pharmaceutical Co., Ltd. Mochida Pharmaceutical Co.,Ltd. Ono Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited ASAHI INTECC CO., LTD. Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company						
Member: Hirokuni Arai			Sumitomo Bakelite Co., Ltd.											
Member: Taishiro Chikamori				Mitsubishi Tanabe Pharma Corporation		Ono Pharmaceutical Co., Ltd. Medtronic Japan Co., Ltd.	MSD K.K. Bayer Yakuhin, Ltd. Sumitomo Dainippon Pharma Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation FUJIFILM RI Pharma Co., Ltd. Takeda Pharmaceutical Company Limited	St. Jude Medical Japan Co., Ltd.					
Member: Hiroyuki Daida				MSD K.K. Amgen Astellas BioPharma K.K. Astellas Pharma Inc. AstraZeneca K.K. Sanofi K.K. Bayer Yakuhin, Ltd. Kowa Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Takeda Pharmaceutical Company Limited		IQVIA Services Japan K.K. St. Jude Medical Japan Co., Ltd. Kowa Pharmaceutical Co., Ltd. Sanwa Kagaku Kenkyusho Co., Ltd. Daiichi Sankyo Company, Limited TOSHIBA MEDICAL SYSTEMS CORPORATION Nihon Medi-Physics Co.,Ltd.	MSD K.K. Actelion Pharmaceuticals Japan Ltd. Astellas Pharma Inc. Abbott Vascular Japan Co., Ltd. Sanofi K.K. St. Jude Medical Japan Co., Ltd. Novartis Pharma K.K. Bayer Yakuhin, Ltd. Pfizer Japan Inc. Shionogi & Co., Ltd. Kowa Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Sumitomo Dainippon Pharma Co., Ltd. Daiichi Sankyo Company, Limited Teijin Pharma Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited	Philips Respironics GK. Fukuda Denshi Co., Ltd ResMed					
Member: Kiyoshi Doi							COVIDIEN JAPAN INC. Johnson & Johnson K.K. TANAC Co., Ltd. Senko Medical Instrument Mfg. Co., Ltd. Takeda Pharmaceutical Company Limited Eli Lilly Japan K.K. W. L. Gore & Associates G.K.						

Name	Personal									Spouse, 1st-degree family member, or any other person with whom the person shares income/asset			Principal/employer (when the person is a member of the research team headed by the principal/employer)	
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Collaborator: Shigeru Miyagawa				TERUMO CORPORATION									TERUMO CORPORATION	TERUMO CORPORATION
Collaborator: Hiromasa Otake				Abbott Vascular Japan Co., Ltd. Goodman Co.,LTD. Sanofi K.K. TERUMO CORPORATION Nipro Corporation HeartFlow Japan G.K. Micron, Inc.										
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Name	Personal									Spouse, 1st-degree family member, or any other person with whom the person shares income/asset			Principal/employer (when the person is a member of the research team headed by the principal/employer)	
	Consultancy	Equity	Patent royalty	Speaking fee	Manuscript fee	Research grant	Scholarship fund	Endowment course	Other	Consultancy	Stock	Patent	Research grant	Scholarship fund
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Name	Personal									Spouse, 1st-degree family member, or any other person with whom the person shares income/asset			Principal/employer (when the person is a member of the research team headed by the principal/employer)	
	Consultancy	Equity	Patent royalty	Speaking fee	Manuscript fee	Research grant	Scholarship fund	Endowment course	Other	Consultancy	Stock	Patent	Research grant	Scholarship fund
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Member: Junjiro Kobayashi
Member: Takayuki Ohno
Member: Yukio Ozaki
Member: Hirofumi Takemura
Member: Hitoshi Yokoyama
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Collaborator: Tomohiro Mizuno
Collaborator: Noboru Motomura
Collaborator: Satoshi Numata
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Collaborator: Hirotaka Oda
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Independent Assessment Committee: Yoshitaka Okamura
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